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# A COMPARATIVE STUDY OF THE RATE OF ATROPHY OF SKELETAL MUSCLE FOLLOWING ANTERIOR RAMISECTION AND ACUTE ANTERIOR POLIOMYELITIS IN THE RHESUS MONKEY

## With a Note on the Weight of the Sartorius Muscle in the Normal Animal

R. E. M. BOWDEN*

*Royal Free Hospital School of Medicine, London, England*

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### INTRODUCTION

Although the histological changes following experimental poliomyelitis have been reported by several observers, there does not appear to have been any quantitative study of atrophy following this disease. It therefore seemed that a comparison of the rate of atrophy following anterior ramisection and acute anterior poliomyelitis might be useful from two points of view. Firstly, any striking differences might shed more light on the changes occurring in the affected muscles, particularly in the acute stages of poliomyelitis, and secondly, knowledge of the time course and degree of atrophy is an essential preliminary requirement for experimental evaluation of the various forms of physical therapy now used in the treatment of convalescent patients. While cotton rats are susceptible to poliomyelitis and are more readily available than monkeys, the high mortality rate makes it difficult to obtain a sufficient number of convalescent animals for long term experiments. Rhesus monkeys are therefore more suitable for the study of atrophy following anterior ramisection and that following anterior poliomyelitis.

The rate of atrophy of skeletal muscle which follows denervation, inanition, tenotomy and disuse has been studied extensively in the rat, cat and rabbit by many workers amongst whom are Langley and Kato (1915); Lipschütz and Audova, (1921); Davenport and Ranson, (1930); Fischer, (1939, 1940, 1941, 1948); Hines and Knowlton, (1933); Knowlton and Hines, (1940); Hines, Thompson and Lazere, (1942, 1943); Lazere, Thompson and Hines, (1943);

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Grateful acknowledgment is made to Dr. David Bodian for his help, encouragement and valuable criticisms; to Dr. H. A. Howe and Dr. Bodian for selection of all the animals used in this experiment and for their clinical and histological reports on the nervous system of animals presumed to be normal; and to Dr. Margaret Merrell and Mr. D. A. Sholl for invaluable advice on the statistical treatment of the data.

Gutmann and Guttmann, (1942 and 1944); Kosman, Osborne and Ivy, (1946). On the other hand comparatively little work has been reported on atrophy in the rhesus monkey. Chor and Dolkart, (1936), investigated simple disuse atrophy in 6 rhesus monkeys. The animals were immobilised in a padded body and leg cast and were sacrificed 1, 2, 3, 4, 6 and 10 weeks later. The gastro-soleus muscles of the normal and immobilised limbs were weighed and submitted to chemical and histological analysis. In 1937 Chor, Dolkart and Davenport repeated these investigations using the denervated gastro-soleus muscles of 7 young rhesus monkeys. In addition to characteristic histological changes they found that the rate of atrophy was markedly increased by denervation.

When muscles are denervated by anterior ramisection or division of motor nerves, the normal muscles of the contralateral limb may be used as a control, but in poliomyelitis all four limbs may be involved to varying degrees, and the provision of adequate controls presents a difficult problem. It is impracticable to use paired animals, for even if intracerebral injections of a given strain of virus are made under standardized conditions, the degree and distribution of the paralysis is unpredictable. However, if there were any fairly reliable method of estimating the weight of selected muscles in the normal monkeys at the time of inoculation, it should be possible to calculate the loss of weight that had occurred at varying times after the onset of paralysis. This approach seemed to hold some promise of success, and the sartorius muscle was selected for investigation. This choice was made for several reasons. The muscles supplied by the femoral nerve are not only frequently involved in paralysis, but also the sartorius muscle has the following advantages; its contractions can be seen through the intact skin, it is accessible for electrical stimulation, it can be dissected cleanly with ease, there is a minimum of tendon at the origin and insertion, and its form makes it ideal for histological examination.

This investigation necessarily falls into three parts and these will be described separately. They are:—the preliminary study of the normal sartorius muscle, and correlation of muscle weight with body weight and sitting height; the study of atrophy following anterior ramisection; and that following paralysis due to acute anterior poliomyelitis. The results of the first part are given in the appendix.

## THE RATE OF ATROPHY FOLLOWING ANTERIOR RAMISECTION

### *Material and methods*

Eleven rhesus monkeys were used for this study. The animals were anaesthetized with nembutal and laminectomies were performed under aseptic conditions. According to Sherrington (1892) the femoral nerve in the rhesus monkey is derived from L3, L4 and L5 or L4 and L5 alone, and at times also from L6. Stimulation experiments performed in this labora-

tory suggested that L4, L5 and L6 were the roots mainly concerned. Anterior ramisections were performed on the left side in 5 animals and on the right in 6. The alternation of the side of operation was an attempt to exclude any tendency to left or right sided dominance in the animals. The paralysed limbs were left free but the animals were isolated in small cages for 4–7 days until the wounds were soundly healed; they then went into large cages with other monkeys. They were examined at intervals by the methods described by Bodian (1948). On the day of sacrifice the animals were re-examined, anaesthetized with ether, re-weighed and measured. Biopsies were taken on both sides in most cases from m. gracilis, m. vastus medialis and m. biceps femoris. Their motor nerves and the sciatic and femoral nerves were stimulated electrically and mechanically and the sartorius was examined by eye for the presence of fibrillation. The animals were perfused as described in the appendix, but the 1% acetic acid was omitted from the formol-saline, since this interferes with the staining of motor nerve endings. The incisions in both limbs were sutured with the edges firmly overlapped to prevent dehydration in the refrigerator in which the animals were left for 24 hours. The sartorius, gastrocnemius and tibialis anticus muscles of both sides were dissected out as cleanly as possible and were then weighed (see appendix). The spinal cords were carefully removed and the levels of the divided anterior roots were checked.

*Results*

The data relating to these monkeys are summarized in Table 1. The weight of the paralysed muscles was expressed as a percentage of the contra-lateral muscles and these values were plotted against the time since operation.

(a) The formula first used to compute the curves describing the rate of atrophy in the three muscles was

$$y = K + 10^{a+bx}$$

where $y$ is the percentage weight of the muscle as a whole, $x$ the number of days since operation, and the constant $K$ represents the non-muscle-cell-phase of the whole muscle. The lowest asymptote represented by $K$ was determined by the method of trial and error. From inspection of the points on the graph it appears that the lowest asymptote lies between about 15 and 25. Therefore, these and intermediate values of $K$ were taken, and the value of $(y - K)$ was computed and plotted logarithmically against the time $x$ on an arithmetic scale. The value of $K$ which gave the best approach to a straight line was found to be 23 for m. tibialis anticus and gastrocnemius. In the case of m. sartorius there was some apparent discontinuity of the curve, but the best fit for the first part was found by using $K = 23$. For all three muscles the loss of weight was more rapid initially, but the rate of proportionate decline of the muscle-cell-phase was constant. When the three curves are superimposed no significant difference in the rate of atrophy can be observed (Figure 1).

(b) The use of the formula $y = K + 10^{a+bx}$ is open to some objection which will be discussed later. It was suggested* that a simple logarithmic curve might

*By Mr. D. A. Sholl of University College, London.

TABLE 1

*Data Relating to Monkeys With Anterior Ramisection*

| NO. | SEX | BODY WEIGHT (LBS.) At operation | BODY WEIGHT (LBS.) At death | LEVEL OF ANTERIOR RAMISECTION | PARALYSIS | TIME SINCE OPERATION (DAYS) | CLINICAL DEGREE OF ATROPHY | RESULT OF NERVE STIMULATION | HISTOLOGY | % WEIGHT OF PARALYZED MUSCLES Sartorius | % WEIGHT OF PARALYZED MUSCLES Gastrocnemius | % WEIGHT OF PARALYZED MUSCLES Tibialis Ant. | NOTES | FIBRILLATION |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| F.122 | ♂ | 4.5 | | 4.5.6.7. 1 rootlet of 6 intact | Lt. hip, knee, ankle, foot } 00 | 7 | ?1 | | | 106.18 | 113.4 | 103.6 | General condition poor | Feeble |
| F.830 | ♂ | 5.75 | 5.5 | 4.5.6.7. | Lt. hip, knee, ankle, foot } 00 | 8 | ?1 | −ve | Lt. Vastus medialis and Gracilis degenerating nerve fibers only | 112.19 | 90.61 | 92.83 | Muscle hyperirritable | − |
| F.871 | ♀ | 5.75 | 5.25 | 3.4.5.6.7. | Rt. hip, knee, ankle } 00 ? feeble flicker of toes | 14 | ?1 | −ve | Rt. Gracilis Biceps femoris. No evidence of motor innervation | 77.24 | 87.9 | 89.65 | | + |
| F.513 | ♂ | 5.5 | 4.75 | 3.4.5.6.7. | Rt. hip, knee, ankle, foot } 00 | 30 | 2 | | Lt. Gracilis. No evidence of motor innervation seen | 70.42 | 52.36 | 60.84 | | |
| F.583 | ♀ | 5.5 | | 3.4.5.?6 & ?7. Cord damaged in removal at 6 & 7 | Lt. hip, knee, ankle, foot } 00 | 48 | 1+ | −ve | Rt. Gracilis and Vastus medialis severe partial denervation of motor end plates | 56.85 | 42.67 | 43.66 | Muscles hyperirritable | ++ |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| F.396 | ♂ | 4.5 | 4.25 | 2.3.4.5.6. | Rt. hip ?<br>knee 00<br>ankle<br>foot } 2 | 56 | Thigh 1 | + few fibers of lower ⅓ Sartorius | Severe partial denervation of Rt. Gracilis and Vastus medialis | 38.57 | active | active | | |
| F.872 | ♂ | 4.5 | 4.75 | 3.4.5.6.7. | Rt. hip flexors active.<br>knee<br>ankle } 00<br>foot | 70 | 2+ | −ve | Minor degree of denervation in Lt. Gracilis. Very few fibers only degenerated | 34.34 | 34.4 | 34.5 | On left side of cord marked adhesions. No roots cut | + |
| F.500 | ♂ | 7.5 | 5.75 | 3.4.5.6.7. | Lt. hip flexors active.<br>knee<br>ankle } 0<br>foot | 75 | 2 | −ve | Complete denervation Lt. Gracilis + Vastus medialis. Lt. Biceps femoris innervated | 62.78 | 52.48 | 62.72 | | + |
| F.516 | ♀ | 6.0 | 5.0 | 3.4.5.6.<br>5 & 6 large and equal | Rt. hip flexors active.<br>knee<br>ankle } 0<br>foot | 86 | 3 | −ve | Empty N. Trunks and end plates in Rt. Gracilis and Vastus medialis. Rt. Biceps femoris. No evidence of denervation seen | 58.64 | 65.03 | 85.2 | Lt. leg still weak in early stages | + |
| F.517 | ♀ | 6.5 | 4.0 | 4.5.6.7.<br>4.? rejoined<br>6 & 7 joined together to each other | Lt. hip flexors active.<br>knee<br>ankle } 00<br>foot | 103 | 2+ | + lower ⅓ medial border Sartorius few fibers contracted very narrow strip | Few normal end plates in Gracilis | 50.05 | 25.39 | 25.06 | Poor condition at sacrifice | None seen |
| F.515 | ♀ | 6.0 | 4.5 | 4.5.6.7.<br>4.5.6. adherent<br>7 free | Rt. hip flexors active.<br>? flicker in femoral group.<br>ankle 00<br>toes flexing | 170 | Thigh 2<br>Leg 3 | Sartorius brisk Calf + Tib. Ant. −ve. Toe flexors weak +ve. | Rt. Gracilis Vastus medialis. Biceps femoris. Partial denervation | 102.23 | 23.85 | 29.92 | | None seen |

be used to describe the observations. For each of the three muscles a curve was fitted using the formula

$$y = a + b \log x,$$

where $y$ was the percentage weight of the muscle and $x$ the log of the time. The three curves are plotted together in Figure 2. (The formula $\log y = a + bx$ was found to be inappropriate.)

The slopes of the three curves do not differ significantly from one another, and there was therefore no evidence to suggest that either the rate or degree

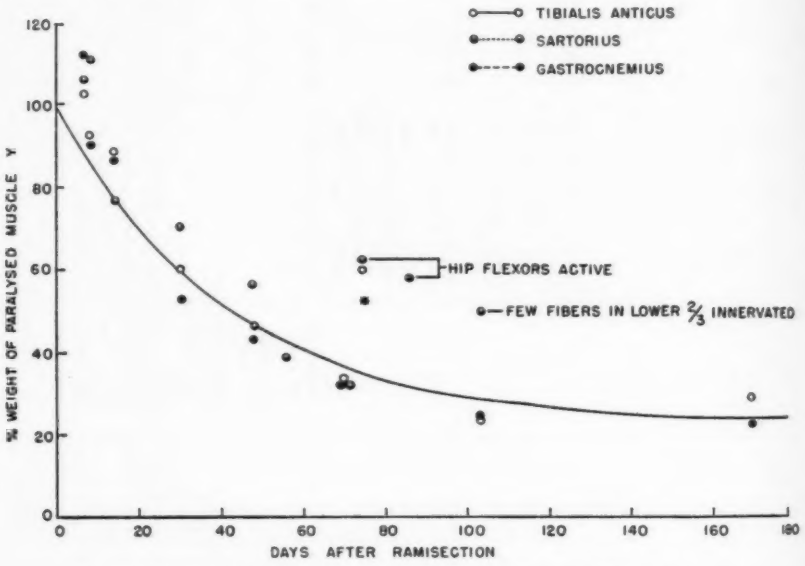


FIG. 1. RATE OF ATROPHY OF MUSCLE IN THE RHESUS MONKEY AFTER ANTERIOR RAMISECTION.

of atrophy differed significantly in the sartorius, gastrocnemius and tibialis anterior.

(c) The residual sum of squares was calculated. In each case the simple logarithmic curve gave the most satisfactory fit to the data.

## *Discussion*

In considering the results of the investigation the question of hypertrophy of the muscles of the normal limb arises. When the weight of the normal sartorius at the time of sacrifice is compared with both the estimated weight of the muscle at the time of operation and the estimated normal weight at sacrifice, no significant alteration in weight was detected in 9 animals and only

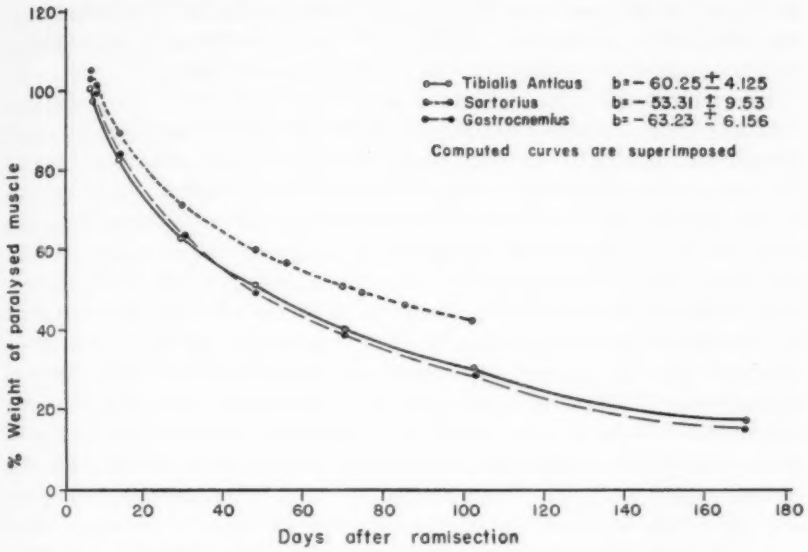


FIG. 2. RATES OF ATROPHY OF MM. SARTORIUS, GASTROCNEMIUS, AND TIBIALIS ANTICUS IN THE RHESUS MONKEY AFTER ANTERIOR RAMISECTION.

TABLE 2

*Sartorius in Normal Limb of Animals with Paralysed Limbs on the Other Side of Body after Anterior Ramisection**

| MONKEY | TIME AFTER RAMISECTION | BODY WT. AT OPERATION | EST. WT NORMAL SARTORIUS MUSCLE FOR BODY WT. AT OPERATION | S.D. OF WT. OF SARTORIUS | BODY WT. AT SACRIFICE | EST. WT. NORMAL SARTORIUS MUSCLE FOR BODY WT. AT SACRIFICE | S.D. OF WT. OF SARTORIUS | ACTUAL WT. OF INNERVATED SARTORIUS AT TIME OF SACRIFICE |
|---|---|---|---|---|---|---|---|---|
| | *days* | *lbs* | *lbs* | | *lbs* | *gms* | | *gms* |
| F-122 | 7 | 4.5 | 1.778 | ±0.4717 | | | | 1.083 |
| F-830 | 8 | 5.75 | 2.65 | ±0.6681 | 5.5 | 2.091 | ±0.6681 | 2.666 |
| F-871 | 14 | 5.75 | 2.65 | ±0.6681 | 5.25 | 2.253 | ±0.5834 | 2.8166 |
| F-513 | 30 | 5.5 | 2.4548 | ±0.6681 | 4.75 | 1.925 | ±0.4717 | 2.1416 |
| F-583 | 48 | 5.5 | 2.4548 | ±0.6681 | | | | 2 125 |
| F-396 | 56 | 4.5 | 1.7779 | ±0.4717 | 4.25 | 1.647 | ±0.5135 | 0.675 |
| F-872 | 70 | 4.5 | 1.778 | ±0.4717 | 4.75 | 1.925 | ±0.4717 | 2.9 |
| F-500 | 75 | 7.5 | 4.6194 | ±2.6321 | 5.75 | 2.65 | ±0.6681 | 3.45 |
| F-516 | 86 | 6.0 | 2.886 | ±0.415 | 5.0 | 2.091 | ±0.5834 | 2.5 |
| F-517 | 103 | 6.5 | 3.388 | ±0.8518 | 4.0 | 1.5157 | ±0.5135 | 1.733 |
| F-515 | 170 | 6.0 | 2.886 | ±0.415 | 4.5 | 1.778 | ±0.4717 | 3.0 |

* The actual weight of the healthy muscle at the time of sacrifice should be compared with the estimated weights calculated on the bases of body weight at the time of operation and of sacrifice. No unequivocal evidence of hypertrophy is found.

a slight increase was found in F-515 and F-872 (both long term cases, Table 2). However, the wide range of variability in the normal is such that this nega-

tive result might mask true hypertrophy, but histological examination and measurement of muscle fiber diameters showed no evidence of hypertrophy. The histological data will be reported in detail at a later date.

The constant ($K = 23$) used in the formula $y = K + 10^{a+bx}$ was derived by trial and error. In theory this represents the percentage weight of the non-contractile and supporting tissue of the muscle, the fat, vessels and nerves, but it is doubtful whether, in view of its derivation, any definite physiological significance should be attached to it here. From their own observations, and those of others, Hines and Knowlton (1933) gave the percentage of non-muscle-cell-phase of skeletal muscle as 10–20% in the rat. In this and other experiments on the rate of atrophy of muscle in the adult rat, they assumed the non-muscle-cell-phase to be 15% of the total weight of the tissue. In 1939 Hines and Knowlton investigated the effect of age upon the cellular phases of skeletal muscle in the rat, and found that this ranged from 40% in young animals to 15% in mature ones. Lowry, Hastings, Hull and Brown (1942) studied the histochemical changes associated with aging in the skeletal and cardiac muscle of the rat. Their findings are at variance with those of Hines and Knowlton, and there is, therefore, some confusion on the matter. There is a second objection to the use of the parameter $K$, for histological observations suggest that there might be not only a relative increase of connective tissue due to atrophy of the contractile tissues, but also an absolute increase in the fibrous tissue. These objections can be overcome in this experiment, for the simple logarithmic curve gives the best description of the data, and it is therefore the one of choice. However, extrapolation beyond the observations is not permissible and no predictions can be made beyond these points. It is clear that no estimate of the proportion of non-contractile tissue can be made.

The evidence presented here would suggest that the rate of atrophy in the plantar flexors and dorsiflexors is similar and also does not differ significantly from that of m. sartorius. Eccles (1944) found that in disuse the atrophy of plantar flexors and dorsiflexors proceeded at different rates in the cat, *provided the muscles were maintained under identical mechanical conditions*. In the experiment reported here identical conditions did not prevail as the limbs were left free and the muscles were subjected to constant alterations in length by passive movements and by the effect of gravity with alterations of position and activity of the monkeys. Furthermore, it must be remembered that relatively few animals were available for this present study. It is of interest to note that in F-500 and F-516 stimulation of the nerve to sartorius failed to elicit a contraction, but the flexors of the hip had recovered and active movements of this joint were constantly occurring. In F-517 a few fibers on the lower $\frac{2}{3}$ of the medial border of the muscle contracted on stimulation of the nerve.

Inspection of the data suggests that there might be some initial increase of weight of the paralysed muscles. This might possibly be due to intramuscular edema for which there is some evidence in the histological study. The same suggestion of an initial increase of weight is found on inspection of the material presented by Lipschütz and Audova (1921) who investigated the rate of atrophy of the calf muscle in the rabbit after division of the sciatic nerve. Such an initial rise of weight has not been observed by Fischer or by Hines and his colleagues who have investigated very large numbers of rats. Since the time course of atrophy is more rapid in the rat than in the rabbit or monkey, there is a chance, admittedly remote, that this might have escaped detection. However, the apparent increase in weight observed here is within the ranges of variability of the normal, and no evidence of an abnormal increase in weight is found in this particular experiment.

Since the animals were kept in small cages during the first 4–7 days after operation, it might be argued that some degree of atrophy due to denervation was masked by disuse atrophy in the normal muscles of the early cases reported here. Although there is no competition for food in small cages, activity is known to vary considerably with the individual monkeys, and this factor which cannot be assessed accurately, is probably not significant.

The time course of the atrophy of denervation described by Chor, Dolkart and Davenport (1937) appears to differ slightly from that observed in this experiment. In the cases reported by Chor, et al., the gastro-soleus muscles had lost about 88% of the normal weight at 84 days. The greater degree of atrophy might possibly be due to the pressure of the cast and to immobilization. Chor, Cleveland, Davenport, Dolkart and Beard (1939), Huddleson (1944), and Jackson (1945) have presented evidence to show that atrophy of denervation is increased by immobilization. Hines (1942) on the other hand found that the rate of recovery was retarded by immobilization but considered that the rate of atrophy was not affected.

## *Conclusions*

In this experiment the rates of atrophy of the sartorius, gastrocnemius and tibialis anticus muscles were found to be similar after anterior ramisection. There was no evidence of hypertrophy of the sartorius muscle of the contralateral limb. The rates of decline of muscle weight were best described by curves computed by using the formula

$$y = a + \log x$$

where $y$ = the percentage weight of the muscle as a whole, and $x$ the time since operation. In order to insure complete denervation of sartorius, L2–L7 inclusive should be cut.

TABLE 3

*Percentage Weight of completely Paralyzed Sartorius Muscles in Rhesus Monkeys after Poliomyelitis*

Based on actual or calculated body weight at inoculation

| MONKEY | CONDITION AT TIME OF INOCULATION | | DURATION OF PARALYSIS | HEIGHT | BODY WT. | | ESTIMATED WT. OF NORMAL SARTORIUS | WT. OF PARALYZED SARTORIUS | | $\frac{\text{WT. OF PARALYZED MUSCLE}}{\text{CALCULATED WT. OF NORMAL MUSCLE}} \times 100$ | | MEAN % WT. OF PARALYZED MUSCLES |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Nutrition | Wt. | | | calculated | actual at death | | R | L | R | L | |
| | | *lbs* | *days* | *ins* | *lbs* | | *gms* | *gms* | | | | |
| F 503 | G | | 1 | 14.0 | 6.05 | 6 | 2.93 | 3.0 | 3.03 | 102.56 | 103.59 | |
| 896 | F | | 1 | 14.25 | 5.9 | 4.7 | 2.77 | 2.25 | 1.56 | 81.22 | 56.24 | |
| 981 | G | | 1 | 12.75 | 4.67 | 5.0 | 1.87 | 2.5 | 2.9 | 133.6 | 155.0 | |
| 982 | F | | 1 | 13.875 | 5.45 | 5.0 | 2.4 | 2.08 | 1.85 | 86.78 | 77.08 | |
| G 163 | P | 5 | 1 | 13.75 | 4.68 | 4.5 | 2.092 | 2.34 | 2.23 | 111.98 | 106.4 | |
| 168 | P | 4 | 1 | 12.75 | 3.7 | 4.0 | 1.52 | 3.0 | 3.05 | 197.92 | 200.96 | 117.78 |
| F 671 | G | 7 | 2 | 13.875 | 5.9 | 6.25 | 3.98 | 2.98 | 2.88 | 79.89 | 72.38 | 76.14 |
| F 503 | G | | 3 | 14.0 | 6.05 | 6.0 | 2.93 | 3.0 | | 102.56 | | |
| 666 | F | 6.25 | 3 | 14.25 | 5.95 | 4.75 | 3.1 | 2.1 | 2.083 | 67.74 | 67.19 | 79.16 |
| G 630 | | | 4 | 12.5 | 4.18 | | 1.575 | 0.883 | 0.842 | 56.06 | 53.43 | |
| 489 | | | 4 | 12.5 | 4.18 | | 1.575 | 1.658 | 1.7 | 102.57 | 107.94 | |
| F 449 | G | | 4 | 13.5 | 5.5 | 4.0 | 2.45 | 1.73 | 1.7 | 70.61 | 69.39 | |
| G 601 | | | 4 | 12.75 | 4.48 | 3.75 | 1.775 | 1.6 | 1.725 | 90.14 | 97.18 | 80.92 |
| F 663 | G | 7.5 | 5 | 15.125 | 7.28 | 6.75 | 4.619 | | 2.842 | | 61.52 | |
| 668 | G | 6.25 | 5 | 14.125 | 6.18 | 5 | 3.1 | 2.7 | 2.7 | 87.09 | 87.09 | |
| 670 | G | 6 | 5 | 13.75 | 5.78 | 5.5 | 2.886 | 2.883 | | 99.89 | | |
| 423 | G | | 5 | 12.875 | 4.8 | 4.0 | 1.975 | 1.55 | 1.658 | 78.48 | 83.95 | |
| 931 | P | | 5 | 15.75 | 6.6 | 5.5 | 3.475 | 3.075 | | 88.49 | | 83.79 |
| F 427 | G | | 7 | 13.75 | 5.78 | | 2.65 | 2.58 | 2.59 | 95.47 | 97.73 | 96.6 |
| F 925 | F | | 12 | 15.125 | 6.85 | 5.5 | 3.775 | 2.116 | 2.2 | 56.05 | 58.28 | 57.17 |
| F 594 | G | 6.5 | 14 | 14.5 | 6.6 | | 3.475 | 3.083 | 3.15 | 88.72 | 90.65 | 89.69 |
| G 452 | P | | 16 | 13.0 | 3.93 | 4 | 1.46 | 1.342 | 1.375 | 91.89 | 94.18 | |
| 258 | F | | 16 | 13.75 | 5.3 | 3.75 | 2.3 | 1.167 | 1.183 | 50.73 | 51.34 | 72.64 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 258 | F | | 16 | 13.75 | 5.3 | 3.75 | 2.3 | 1.167 | 1.183 | 50.73 | 51.34 | 72.64 |
| F 971 | F | | 23 | 14.75 | 6.6 | 5 | 3.475 | 0.93 | 1.1 | 26.76 | 31.68 | 29.2 |
| G 500 | | | 32 | 13.25 | 5.05 | 3.5 | 2.125 | | 0.75 | | 35.29 | 35.29 |
| F 408 | G | | 33 | 14.0 | 6.05 | | 2.925 | 0.633 | 0.708 | 21.64 | 24.21 | 22.93 |
| F 497 | F | | 36 | 13.75 | 5.6 | 3.5 | 2.525 | 1.33 | 1.266 | 52.67 | 50.13 | 51.4 |
| F 492 | G | | 46 | 13.25 | 5.2 | | 2.225 | 0.716 | 0.75 | 32.7 | 33.7 | 33.2 |
| F 700 | G | 5 | 52 | 13.5 | 5.5 | 3.5 | 2.09 | 0.55 | 0.75 | 26.31 | 35.88 | 31.09 |
| F 664 | G | 5.5 | 53 | 13.25 | 5.2 | 3.75 | 2.455 | 1.042 | | 42.43 | | 42.43 |
| F 472 | G | | 58 | 14.875 | 7.03 | 6.0 | 3.95 | | 1.516 | | 38.28 | 38.28 |
| F 321 | G | | 60 | 14.125 | 6.2 | 4.5 | 3.075 | 0.775 | 0.285 | 25.2 | 9.25 | |
| 664 | G | | 60 | 13.25 | 5.2 | 3.75 | 2.455 | | 1.092 | | 44.48 | 26.31 |
| F 437 | G | | 61 | 14.0 | 6.05 | | 2.925 | 0.4 | 0.45 | 13.68 | 15.38 | 14.53 |
| F 701 | G | 5.5 | 70 | 13.5 | 5.5 | 5.0 | 2.455 | 1.55 | 1.642 | 63.1 | 66.87 | 64.99 |
| G 187 | | | 80 | 13.5 | 5.35 | 4.5 | 2.33 | 1.25 | 1.175 | 53.65 | 50.43 | 52.04 |
| G 190 | | | 99 | 12.75 | 4.48 | 2.5 | 1.76 | 0.25 | 0.208 | 14.21 | 11.84 | 13.025 |
| G 115 | | | 106 | 15.125 | 7.18 | 3.25 | 4.15 | 0.475 | 1.1 | 14.45 | 26.51 | 20.48 |
| F 435 | G | | 142 | 13.125 | 5.07 | 3.75 | 2.13 | | 0.733 | | 34.4 | 34.4 |
| F 343 | G | | 164 | 13.0 | 4.95 | 4.5 | 2.05 | 0.8 | | 39.02 | | 39.02 |

G—Good; F—Fair; P—Poor.

## THE RATE OF ATROPHY OF THE SARTORIUS MUSCLE AFTER ANTERIOR POLIOMYELITIS

### *Material and Methods*

Forty animals with clinically complete paralysis of the hip flexors and quadriceps group of muscles on one or both sides of the body were available for this investigation. Seventy completely paralysed muscles were suitable for study. The animals had been systematically examined for the first signs of disease after inoculation and the progress of the paralysis was also checked. The time of onset of complete paralysis was known accurately to within one day. The animals were re-examined at intervals and also on the day of sacrifice before and during the induction of anaesthesia by ether. Sometimes activity which had not been detected clinically was revealed during the induction. If this were so, these muscles were excluded from this study.

Ideally the weight of every animal should have been measured at the time of inoculation, but for various reasons this was not always practicable. Of 211 monkeys weighed at this time only 11 proved suitable for the investigation. The sitting height and body weight were measured at the time of sacrifice and in some cases the muscles were exposed and stimulated directly and indirectly with induction shocks. In the latter circumstances the skin was firmly sutured after the examination. The animals were then perfused as already described, usually with aceto-formol solution, because the central nervous system was required for another investigation, and the muscles were dissected out 24 hours later.

The weight of the animal at the time of death was no reliable indication of the weight of the normal animal. Some of these animals were prostrated by severe generalized paralysis and in all animals, other muscle groups were affected by the disease. The degree of atrophy of all paralysed or paretic muscles influenced the body weight, but not the sitting height. Therefore, in those cases where the normal body weight was unknown, this was estimated by reference to the regression lines of body weight upon height (see appendix). The state of nutrition of the animal at the time of inoculation was usually recorded, but where this had been omitted the line computed for the combined group of those in good and fair condition was used.

The estimated weight of the normal sartorius was then obtained by reference to the regression curve computed for the correlation of muscle weight and body weight. Where the body weight at the time of inoculation was known, this was used instead of the estimated body weight. The weight of the paralysed sartorius was expressed as a percentage of the estimated weight of the normal muscle. This percentage was plotted against the time since the onset of clinically complete paralysis.

### *Results*

The data are given in Table 3 and are shown graphically in Figure 3. The curve describing the rate of atrophy was computed using the formula

$$y = a + b \log x$$

when $y$ = the percentage weight of the whole muscle and $x$ = time since the onset of *complete* paralysis.

There is marked scatter of the points, particularly in the early stages. In some animals the weight of the paralysed muscle is apparently increased beyond the normal range of variation. However, where the means of these

percentages are taken (see last column of Table 3 and Figure 4) the apparent increase in weight lies just within the limits of normal variation. There was no statistically significant difference between the slope of the curves computed

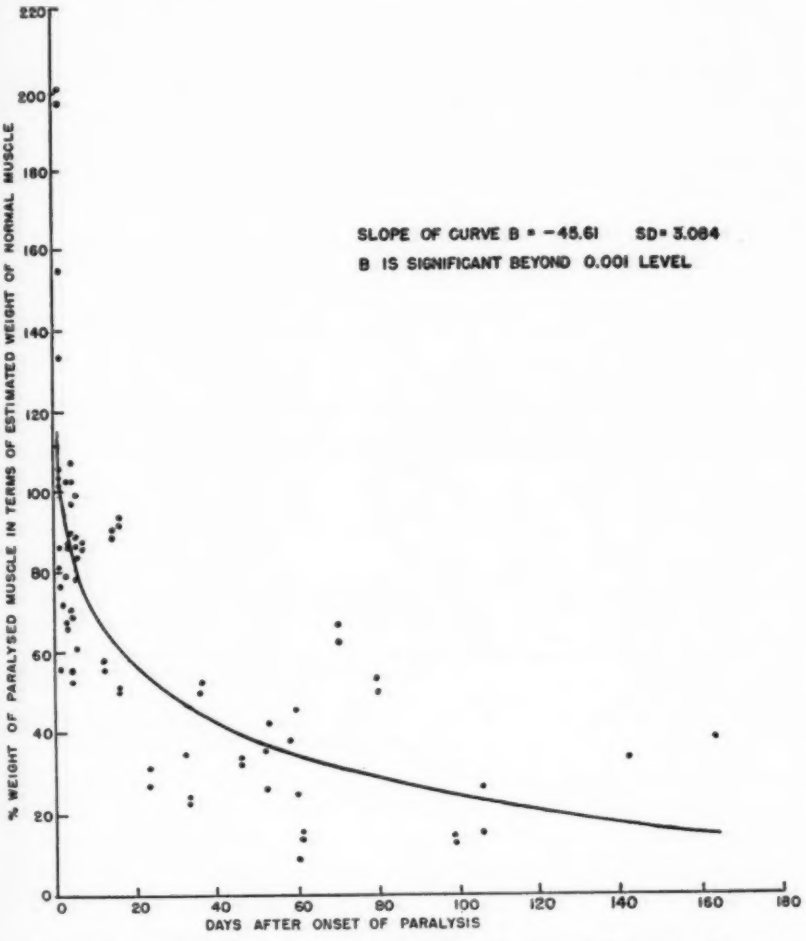


FIG. 3. THE RATE OF ATROPHY OF COMPLETELY PARALYSED SARTORIUS M. OF THE RHESUS MONKEY IN ANTERIOR POLIOMYELITIS.

for the rates of atrophy of the sartorius muscle after anterior ramisection and after poliomyelitis (Figure 5).

An attempt was made to gauge the error introduced by estimating the normal body weight at the time of inoculation. The weights of 11 animals

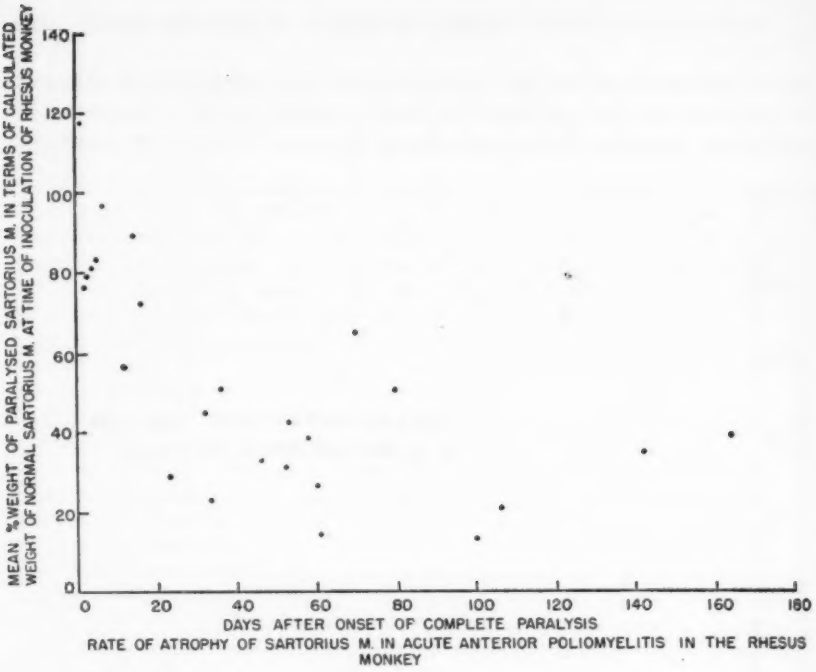


FIG. 4

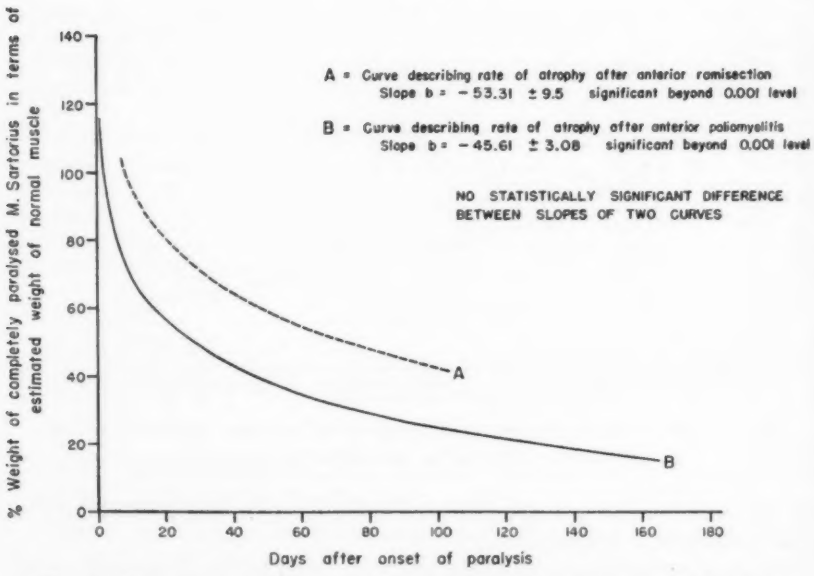


FIG. 5. COMPARISON OF RATES OF ATROPHY OF M. SARTORIUS IN THE RHESUS MONKEY AFTER ANTERIOR RAMISECTION AND ANTERIOR POLIOMYELITIS.

were known, and are given with the estimated weight in Table 4. The percentage error has been calculated in each case and the mean error for the group is 5.56 (S.D. ±0.48; S.E. ±0.14). The mean percentage error in the muscle weights is 9.15.

## *Discussion*

The use of the actual body weight of the animal at the time of sacrifice is open to objection, since atrophy of many muscle groups has contributed to this weight. However, the estimation of normal body weight is also open to criticism, since it introduces a source of error, which was of the order of 5.6% ± 0.5. On general considerations, it seems sounder to use the weight of

TABLE 4

*Percentage Error of Estimated Body Weight on Known Weight*

| MONKEY | KNOWN PREOPERATIVE WEIGHT | CALCULATED WEIGHT | ERROR | % ERROR ON KNOWN WEIGHT |
|---|---|---|---|---|
| | *lbs* | *lbs* | *lbs* | |
| F-671 | 7 | 5.9 | −1.1 | −15.71 |
| F-666 | 6.25 | 5.9 | −0.35 | −5.6 |
| F-663 | 7.5 | 7.275 | −0.225 | −3.0 |
| F-668 | 6.25 | 6.175 | −0.075 | −1.2 |
| F-670 | 6.0 | 5.775 | −0.225 | −3.75 |
| F-594 | 6.5 | 6.6 | +0.1 | +1.54 |
| F-700 | 5.0 | 5.5 | +0.5 | +10.0 |
| F-664 | 5.5 | 5.2 | −0.3 | −5.45 |
| F-701 | 5.5 | 5.5 | 0.0 | 0.0 |
| G-163 | 5.0 | 4.68 | −0.32 | −6.4 |
| G-168 | 4.0 | 3.7 | −0.3 | −8.5 |

Body weight mean % error = 5.56 S.D. ±0.48
S.E. of mean ±0.14
Muscle wt. mean % error = 9.15

the normal animal rather than the weight of the paralysed animal as a basis for the calculations, even though circumstances made it necessary to estimate the normal weight in the majority of animals. There is no question that the known normal body weight should be used rather than the estimated weight.

The scatter of the points in Figure 3 may be due to several factors. The method of estimation of the normal weight of both the body and muscle weight introduces possible errors. Also the pathological lesions in the cord are such that at least 5–10% of the motor nerve cell population may remain intact although the limbs supplied by those segments are totally paralysed as judged by all clinical examinations (Bodian, 1948). In this study electromyographical examinations were not practicable and minor degrees of innervation cannot be excluded. (Histological examination of some of these muscles

will be reported later.) In addition, if there is a marked disparity in the rate of denervation and disuse atrophy in the monkey, another factor comes into play. It is known that a certain high proportion of paretic and paralysed muscles recover spontaneously in time; the anterior horn cells are temporarily affected and impulses fail to reach the muscles, or in other cases the anterior horn cells are undamaged but the internuncial neurones have been affected (Bodian, 1948). The presence of innervated muscle fibers might well influence the rate of atrophy and contribute to the scatter of points shown in Figures 3 and 4.

Unfortunately there were few cases of long duration available for this experiment since the animals with totally paralysed limbs were usually extremely ill and could not be maintained in an adequate state of nutrition through the acute to the convalescent stages; and secondly, in those who survived the acute stage the majority of paralysed limbs showed some signs of recovery and thus made the animals unsuitable for this study. It is not possible therefore to have any comparable estimate of the degree of scatter in later stages of complete paralysis.

There are other factors which merit consideration although at present their significance cannot be adequately assessed. The animals with poliomyelitis were mostly immobilized by widespread, severe paralysis in the first 3–4 weeks, and the effects of pressure and immobility may well be significant; in addition, they were febrile in the acute stage and there may have been some difficulty in maintaining nutrition. The influence of these variable factors cannot be determined precisely. In contrast, the animals paralysed by ramisection had no constitutional disease and the paralysed limbs were being constantly subjected to passive movement and change of position as a result of the animals' activities. Chor, Cleveland, Davenport, Dolkart and Beard (1939) found that passive movement and massage were of benefit in the treatment of paralysed muscle in the monkey, but there is still considerable controversy about the value of such measures.

Lastly there is another factor which should be mentioned; in poliomyelitis the muscle spindles appear to be either unchanged or highly resistant to any pathological change (Batten, 1897; Carey, Massopust, Zeit and Haushalter, 1944; and unpublished observation). In the cases of ramisection, the spindles were deprived of their motor innervation. However, the influence of the muscle spindle upon the rate of atrophy is unknown and at present there seems no method of assessing the significance of this factor.

## CONCLUSIONS

From data presented here the degrees and rates of atrophy of the sartorius muscle following anterior ramisection and complete paralysis due to experimental poliomyelitis do not appear to differ significantly.

The technique used in this experiment does not allow any definite conclusions to be drawn regarding the presence or absence of an initial increase in the weight of the muscles paralysed as a result of poliomyelitis. Such an increase might be found if an inflammatory lesion were present in the muscles themselves, or if there were an acute edema due to vasomotor paralysis.

## SUMMARY

1. The rates of atrophy of m. sartorius, gastrocnemius and tibialis anticus have been studied in 11 monkeys after anterior ramisection. In all three muscles the rate appears to be similar. Curves describing the rate of atrophy were computed by using the formulae

$$\text{a) } y = K + 10^{a+bx}$$

where $y$ = total percent weight of muscle, $K$ = a constant representing the non-muscle-cell-phase of the tissues and $x$ = the time since operation.

$$\text{b) } y = a + b \log x$$

where $y$ = total percent weight of muscle and $x$ = time since operation.

The merits of the two formulae are discussed, and since the simple logarithmic curve gives the best fit to the observed points, this was considered to be the one of choice.

2. An attempt has been made to study the rate of atrophy of the sartorius muscle in 40 cases of anterior poliomyelitis. Seventy muscles were available for study and in all cases they were completely paralysed as judged by clinical tests and by stimulation of the motor nerve in some cases. The calculations are based upon an estimation of the weight of the muscle in the normal animal at the time of inoculation of the virus. The method has limitations which are discussed. The rate of atrophy was computed by using the formula $Y = a + bx$ as above.

3. The degree and rate of atrophy of the sartorius muscle after poliomyelitis do not appear to differ significantly from those found following anterior ramisection.

## APPENDIX

### THE WEIGHT OF THE SARTORIUS MUSCLE IN NORMAL RHESUS MONKEYS

#### *Material*

Ninety-one rhesus monkeys were used in this part of the investigation. These animals had either had intracerebral or intranasal inoculations of various strains of the virus of poliomyelitis. They were presumed to be normal since they failed to show any clinical signs of generalized illness, tremor, weakness, inco-ordination, spasticity or paralysis. In every case the central nervous system was examined histologically and in five animals mild signs of sub-

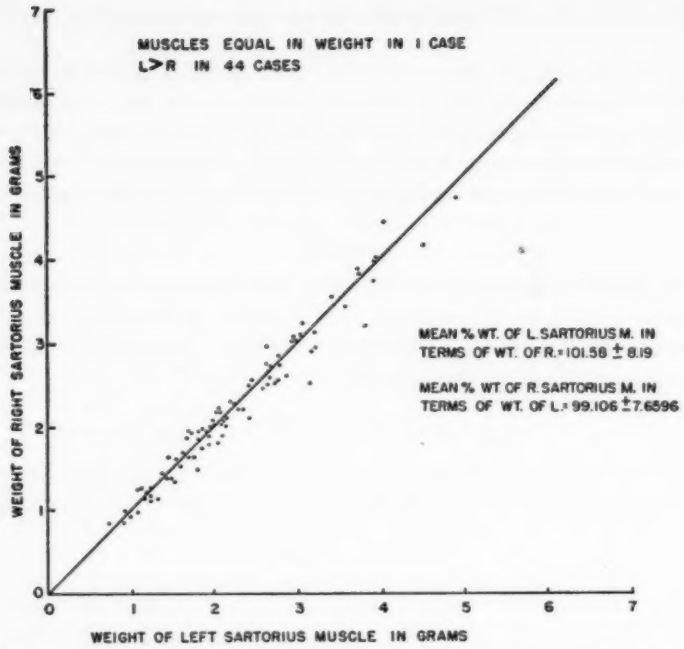
MUSCLES EQUAL IN WEIGHT IN 1 CASE
L>R IN 44 CASES
MEAN % WT. OF L. SARTORIUS M. IN TERMS OF WT. OF R. = 101.58 ± 8.19
MEAN % WT OF R. SARTORIUS M. IN TERMS OF WT. OF L. = 99.106 ± 7.6596
WEIGHT OF RIGHT SARTORIUS MUSCLE IN GRAMS
WEIGHT OF LEFT SARTORIUS MUSCLE IN GRAMS
0
1
2
3
4
5
6
7

FIG. 6. SCATTER DIAGRAM FOR WEIGHT OF L. AND R. SARTORIUS M. IN 86 NORMAL RHESUS MONKEYS.

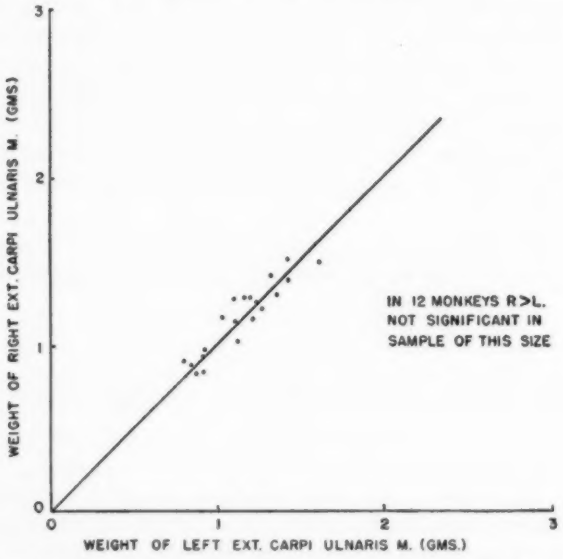


FIG. 7. SCATTER DIAGRAM OF WEIGHT OF EXT. CARPI ULNARIS M. IN 20 NORMAL RHESUS MONKEYS.

clinical disease were found. The final analysis was therefore carried out on the remaining eighty-six animals.

The age of these animals could not be determined precisely as they had not been born in captivity. From data given by Schultz (1933) their ages were estimated to range from 11–36 months with the majority being between 18–24 months. (The rhesus monkey reaches full

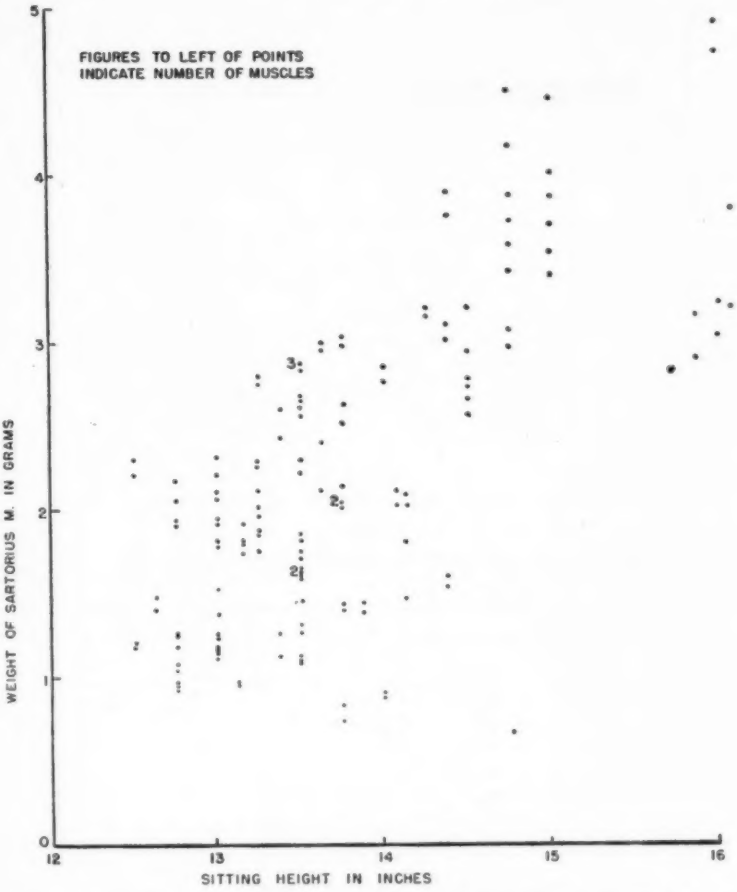


FIG. 8. CORRELATION OF SETTING HEIGHT AND WEIGHT OF SARTORIUS M. 86 NORMAL RHESUS MONKEYS.

maturity at about 48 months of age.) There were forty-three males and forty-three females in this group.

## *Method*

At the time of sacrifice the anaesthetized animals were weighed to the nearest quarter pound and the sitting height was measured to the nearest $\frac{1}{8}$ inch. The animals were perfused

through the aorta with about 50 ml of normal saline followed by 1–2 liters of 10% formol-saline containing 1% acetic acid. (There was no significant difference in body weight before and after perfusion.) The animals were placed in the refrigerator for 24 hours and the sartorius muscles were then dissected out as cleanly as possible and were weighed in grams to two decimal places. The means of three separate weighings were taken for each muscle.

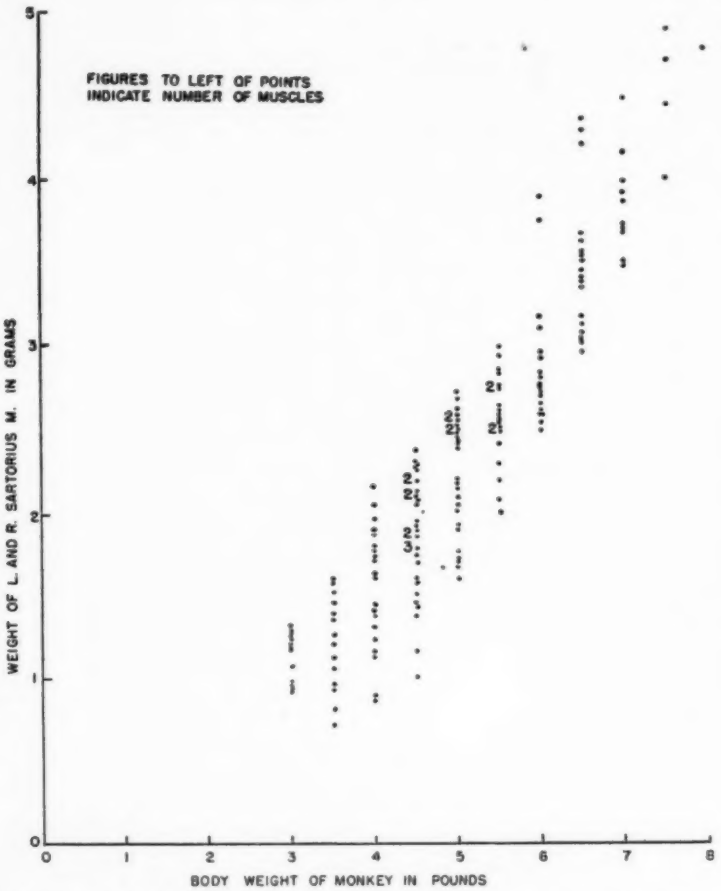


FIG. 9. CORRELATION OF WEIGHT OF SARTORIUS MUSCLES AND BODY WEIGHT OF 86 NORMAL RHESUS MONKEYS.

## *Results*

*Weight of the normal sartorius muscle.* In only one case out of 86 were the weights of the right and left muscles identical. When the weight of the right muscles was expressed as a percentage of the weight of the left, the mean was found to be 99.11%; S.D. ± 7.66. When the weight of the left muscle was expressed as a percentage of the weight of the right, the mean

was 101.6%; S.D. ± 8.19. When a scatter diagram was constructed, there was no evidence of a left or right sided dominance in the group as a whole (Figure 6). In 20 of these monkeys, the extensor carpi ulnaris muscle was also weighed. In 12, the right muscle was heavier than the left (Figure 7). In 12 out of the 20, the arm and leg muscles of greater weight were on the opposite sides of the body. In these 20 monkeys there was no significant evidence of a right or left handed dominance in the group as a whole. It is impossible to exclude the presence of such dominance in the individual.

TABLE 5

*Weight of Sartorius Muscle in Normal Rhesus Monkeys*

| NUMBER OF INDIVIDUALS | GROUPS IN ORDER OF BODY WEIGHT | MEAN OF BODY WEIGHT | S.D. OF MEAN BODY WEIGHT | MEAN WEIGHT OF SARTORIUS MUSCLE | NUMBER OF MUSCLES | S.D. OF MEAN WEIGHT OF MUSCLES |
|---|---|---|---|---|---|---|
| | *lbs* | *lbs* | | *gms* | | |
| 6 | 3.0–3.49 | 3.125 | ±1.304 | 1.13 | 12 | ±0.341 |
| 7 | 3.5–3.99 | 3.571 | ±1.463 | 1.228 | 14 | ±0.440 |
| 10 | 4.0–4.49 | 4.125 | ±1.381 | 1.565 | 20 | ±0.514 |
| 17 | 4.5–4.99 | 4.529 | ±1.135 | 1.881 | 34 | ±0.472 |
| 14 | 5.0–5.49 | 5.0 | 0.0 | 2.174 | 28 | ±0.583 |
| 10 | 5.5–5.99 | 5.525 | ±1.843 | 2.477 | 20 | ±0.668 |
| 7 | 6.0–6.49 | 6.0 | 0.0 | 2.908 | 14 | ±0.415 |
| 9 | 6.5–6.99 | 6.550 | ±2.320 | 3.283 | 18 | ±0.851 |
| 4 | 7.0–7.49 | 7.0 | 0.0 | 3.811 | 8 | ±1.520 |
| 2 | 7.5–7.99 | 7.625 | ±7.628 | 4.527 | 4 | ±2.632 |
| Total 86 | | | | | | |

TABLE 6

*Percent Variations of Muscle Weight Around Mean Muscle Weight*

| BODY WEIGHT IN LBS. | MEAN WEIGHT OF SARTORIUS | STANDARD DEVIATION × 2 | $\frac{\text{SD} \times 2}{\text{MEAN WT.}} \times 100$ |
|---|---|---|---|
| | *gms* | | |
| 3+ | 1.13 | 0.681 | 60.30 |
| 3.5+ | 1.228 | 0.879 | 71.61 |
| 4.0+ | 1.565 | 1.027 | 65.62 |
| 4.5+ | 1.881 | 0.943 | 50.16 |
| 5.0+ | 2.174 | 1.167 | 53.67 |
| 5.5+ | 2.477 | 1.336 | 53.95 |
| 6.0 | 2.908 | 0.915 | 31.52 |
| 6.5+ | 3.283 | 1.704 | 51.89 |
| 7.0+ | 3.811 | 3.139 | 82.36 |
| 7.5+ | 4.527 | 5.264 | 116.29 |

The weight of each muscle was plotted against the sitting height of the monkey, and although there is a definite correlation there is considerable scatter (Figure 8). When the weight of the muscles is plotted against the body weight, the scatter is reduced, although there is still considerable variation of muscle weight amongst individuals of the same body weight (Figure 9). The animals were arranged in half pound groups according to body weight, and the mean weight of each group was plotted against the mean weight of the muscles of these individuals. The points were found to lie on a curve described by the formula

$$y = a + b \log x$$

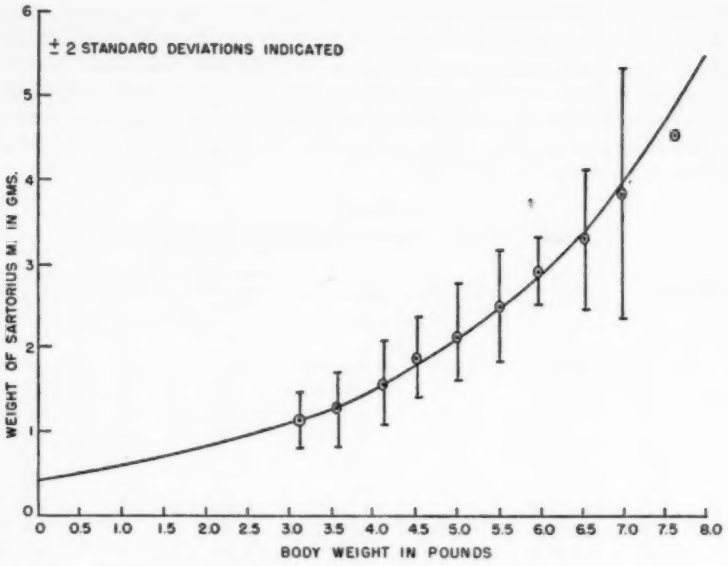


FIG. 10. CORRELATION OF BODY WEIGHT AND WEIGHT OF SARTORIUS MUSCLE IN 86 NORMAL RHESUS MONKEYS.

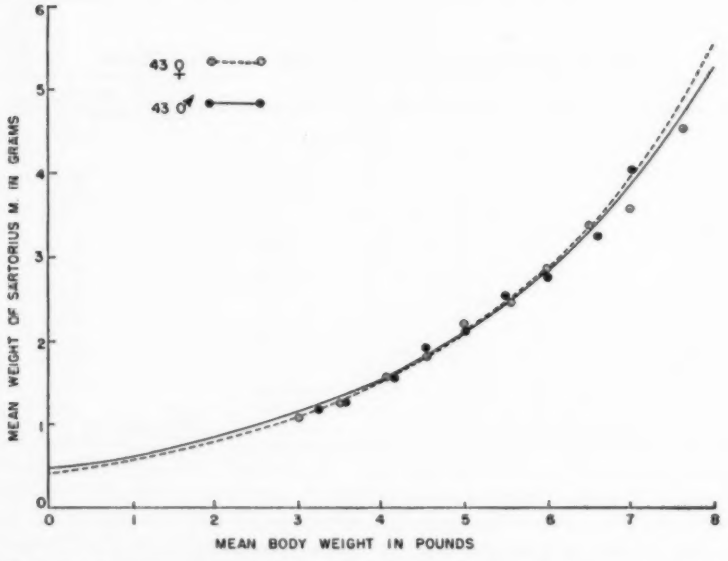


FIG. 11. CORRELATION OF BODY WEIGHT AND WEIGHT OF SARTORIUS M. IN NORMAL RHESUS MONKEYS WITH ANALYSIS OF SEX DIFFERENCES.

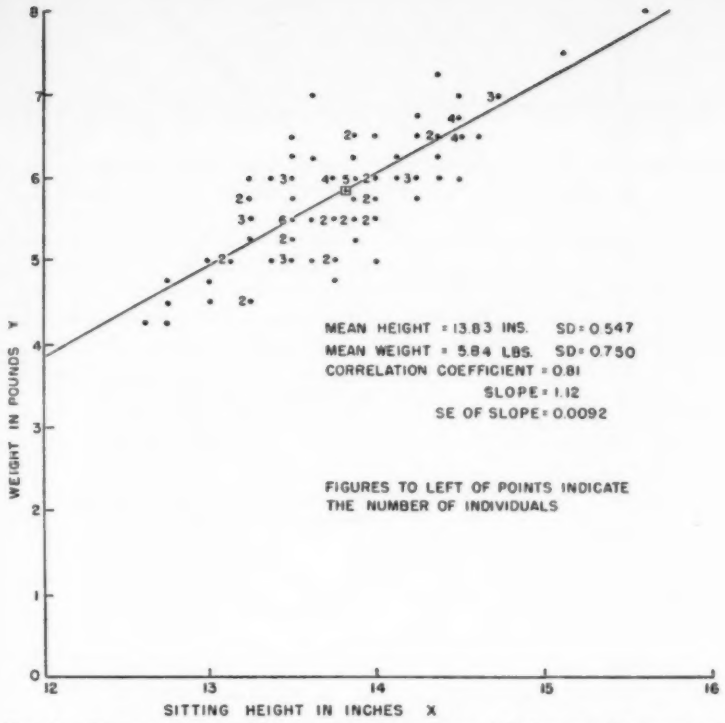
MEAN HEIGHT = 13.83 INS. SD = 0.547
MEAN WEIGHT = 5.84 LBS. SD = 0.750
CORRELATION COEFFICIENT = 0.81
SLOPE = 1.12
SE OF SLOPE = 0.0092
FIGURES TO LEFT OF POINTS INDICATE
THE NUMBER OF INDIVIDUALS
WEIGHT IN POUNDS Y
SITTING HEIGHT IN INCHES X

FIG. 12. CORRELATION OF HEIGHT AND WEIGHT OF 100 RHESUS MONKEYS IN GOOD CONDITION.

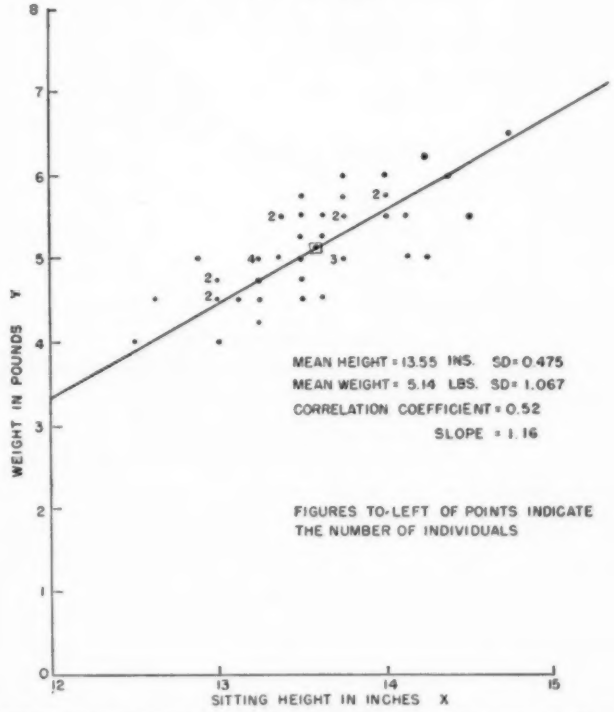
MEAN HEIGHT = 13.55 INS. SD = 0.475
MEAN WEIGHT = 5.14 LBS. SD = 1.067
CORRELATION COEFFICIENT = 0.52
SLOPE = 1.16
FIGURES TO LEFT OF POINTS INDICATE
THE NUMBER OF INDIVIDUALS
WEIGHT IN POUNDS Y
SITTING HEIGHT IN INCHES X

FIG. 13. CORRELATION OF WEIGHT AND HEIGHT OF 46 RHESUS MONKEYS IN FAIR CONDITION.

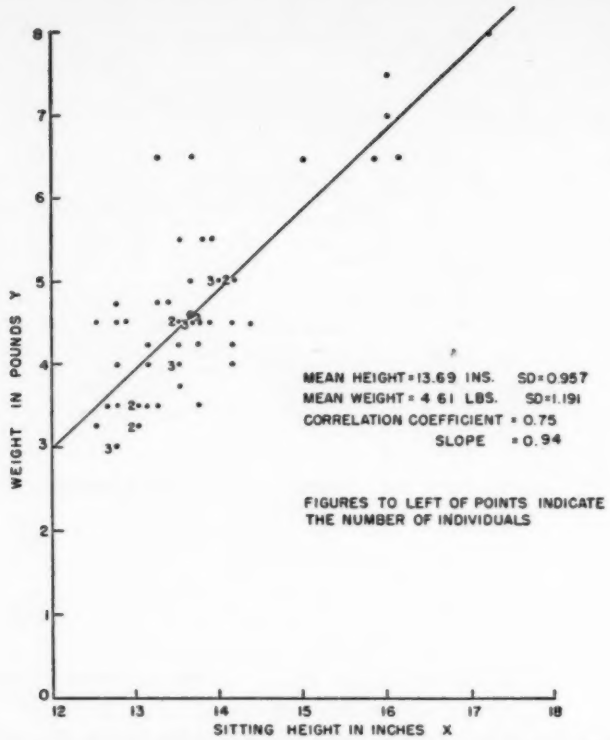
WEIGHT IN POUNDS Y
SITTING HEIGHT IN INCHES X
MEAN HEIGHT = 13.69 INS. SD = 0.957
MEAN WEIGHT = 4 61 LBS. SD = 1.191
CORRELATION COEFFICIENT = 0.75
SLOPE = 0.94
FIGURES TO LEFT OF POINTS INDICATE
THE NUMBER OF INDIVIDUALS

FIG. 14. HEIGHT AND WEIGHT OF 57 RHESUS MONKEYS IN POOR CONDITION.

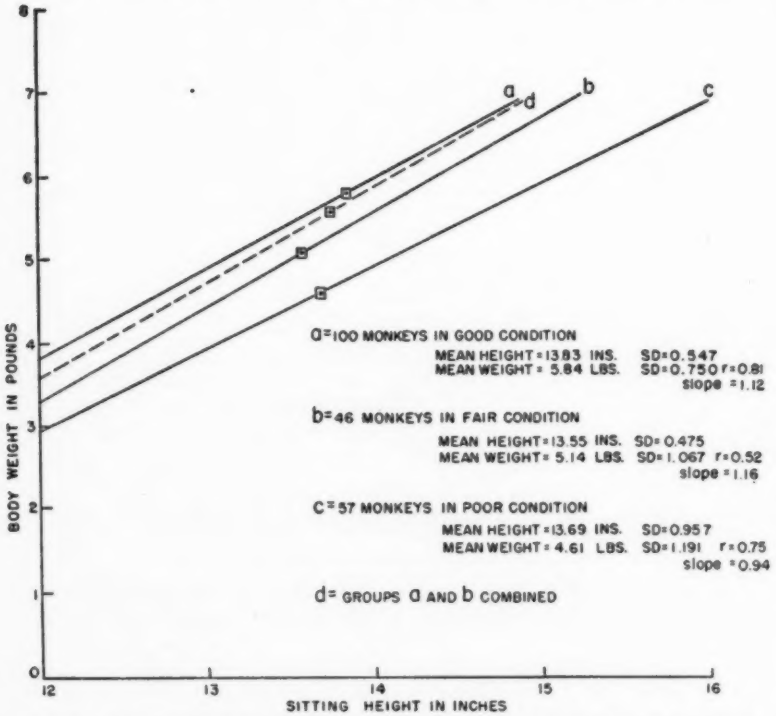
BODY WEIGHT IN POUNDS
SITTING HEIGHT IN INCHES
a
b
c
d
a=100 MONKEYS IN GOOD CONDITION
MEAN HEIGHT = 13.83 INS. SD = 0.547
MEAN WEIGHT = 5.84 LBS. SD = 0.750 r = 0.81
slope = 1.12
b=46 MONKEYS IN FAIR CONDITION
MEAN HEIGHT = 13.55 INS. SD = 0.475
MEAN WEIGHT = 5.14 LBS. SD = 1.067 r = 0.52
slope = 1.16
C=57 MONKEYS IN POOR CONDITION
MEAN HEIGHT = 13.69 INS. SD = 0.957
MEAN WEIGHT = 4.61 LBS. SD = 1.191 r = 0.75
slope = 0.94
d= GROUPS a AND b COMBINED

FIG. 15. CORRELATION OF HEIGHT AND WEIGHT IN NORMAL RHESUS MONKEYS.

where $y$ was the mean weight of muscles and $x$ the mean body weight. Since the number of individuals differed in the groups, acount was taken of this in computing the line. The data are given in Table 5 and Figure 10. The variations within groups are considerable and the percentage variations around the mean weights can be seen by examination of Table 6.

The data for the 43 males and 43 females were treated separately in the same way as the material for the whole group, and again there was considerable individual variation. Regression curves were computed for each sex and no significant difference was found between the curves computed for the sexes (Figure 11), or between these and the one computed for the whole group.

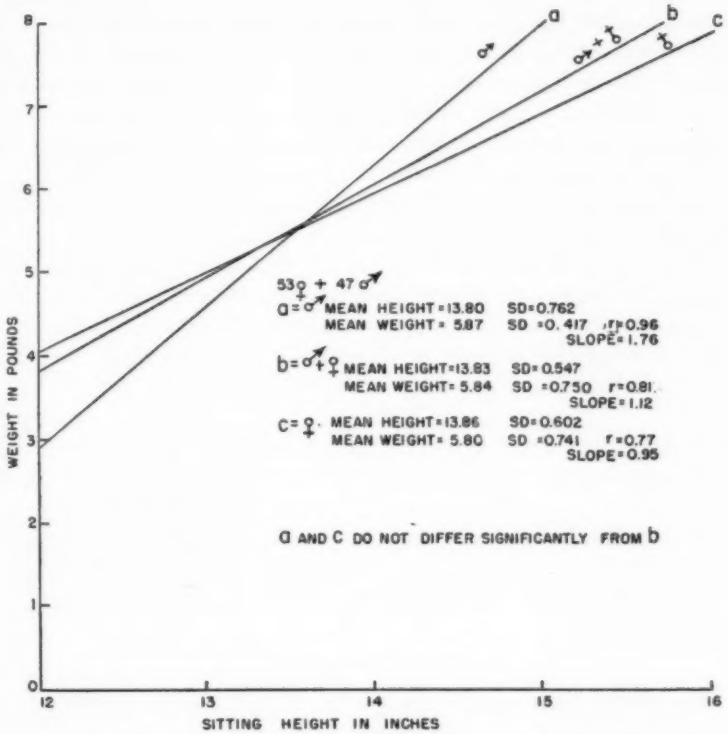


FIG. 16. CORRELATION OF HEIGHT AND WEIGHT WITH ANALYSIS OF SEX DIFFERENCES IN 100 NORMAL RHESUS MONKEYS IN GOOD CONDITION.

*Correlation of sitting height and body weight in normal monkeys.* In addition to the 86 normal monkeys used in the study of muscle weight, the sitting height and body weight were measured in a further 117 animals. The 203 monkeys were divided into three groups according to their state of nutrition. There were 100 monkeys in good condition, 46 in fair and 57 in poor condition.

In group 1 there were 53 females and 47 males; in group 2 there were 28 females and 18 males, and in group 3 there were 33 females and 24 males. The scatter and regression lines for the three groups are shown in Figures 12, 13 and 14. The three regression lines are superimposed in Figure 15 and as might be expected, the weight at any given height tends to be

greater, the better the condition of the animal. In each of the three groups the regression lines were calculated for the two sexes. For monkeys in good condition the regression lines for males and females just differed significantly from each other (Figure 16) but neither differed significantly from the line calculated for the whole group of 100 animals.

## DISCUSSION AND CONCLUSIONS

There is variation between the weight of the right and left sartorius muscles in most monkeys. In the group of 86 animals the majority of muscles were found to vary by not more than 10% of each other but this variation was as high as 20% in a few cases. Lipschütz and Audova (1921) found little variation in weight of the left and right gastro-soleus-plantaris in individual rabbits, the maximum differences being 6.3% and 4.2%. However, their findings were based on a group of only 9 animals. Since the 86 animals in this investigation had previously been inoculated with virus, it might be suggested that the wide variation was due to subclinical disease. However, the clinical history and histological examination of the central nervous system would indicate that this objection might be eliminated.

In the group of 86 animals there was no significant evidence of a right or left sided dominance of the hind limb, but this cannot be excluded for the individual. There was some correlation between muscle weight and sitting height, but correlation is closer between muscle weight and body weight. The correlation between muscle weight and body weight is the same in the two sexes.

There is correlation between sitting height and body weight, and as might be expected, the weight at any given height tends to be influenced by the state of nutrition of the animal. For animals in good condition there was a significant difference between the regression lines of body weight upon sitting height in males and females. The fact that this difference was not demonstrated for animals in fair or poor condition might be due to the smaller numbers involved.

## SUMMARY OF APPENDIX

1. The weight of the sartorius muscle has been studied in 86 normal rhesus monkeys.

a. There may be considerable variation between the muscles of the right and left sides in the same individual. The maximum variation was found to be 20%. A detailed analysis has been made.

b. In the group as a whole there was no evidence of dominance of either the right or left hind limb. Such dominance in the individual cannot be excluded by the data available.

c. There is some correlation between the muscle weight and the sitting height of the individual, but closer correlation exists between muscle weight and body weight. Regression curves have been computed for the whole group

and for the two sexes. No significant difference was found between the relationship of muscle and body weight in these groups. The curves were computed by using the formula

$$y = a + b \log x$$

where $y$ = muscle weight and $x$ = body weight.

2. The correlation between sitting height and body weight has been investigated in 100 monkeys in a good state of nutrition, 46 in a fair state and 57 in a poor state. Regression lines have been computed for each of these groups and each group has been analysed for differences between the sexes.

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# THE CARDIOVASCULAR RESPONSE OF NORMAL YOUNG ADULTS TO EXERCISE AS DETERMINED BY THE DOUBLE MASTER TWO-STEP TEST*

CAROLINE BEDELL THOMAS

WITH THE TECHNICAL ASSISTANCE OF ELEANOR E. STEWART

*Department of Preventive Medicine, The Johns Hopkins University School of Medicine Baltimore, Md.*

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The possible implications of individual variability within the accepted normal or physiologic limits of a given biological characteristic have been all too often overlooked. The concept of average normal values has focussed attention upon the *similarities* of normal human beings, and has largely eliminated the necessity of explaining their *differences* (1). In clinical medicine, where interest and emphasis center in the diseased patient, control studies of normal subjects are usually regarded as a necessary evil; accordingly, most control groups are too small to represent the full extent of the normal physiologic range (2). Human physiological investigations are frequently conducted on small numbers of cooperative and comparatively stable volunteers; where such studies become classical, they are thoughtlessly used as normal standards by others who fail to repeat and extend the original observations (3).

The present paper is part of a broad investigation of normal subjects in which is sought the significance of certain hereditary, physiological and psychological factors as precursors of hypertension and coronary artery disease. The study includes an analysis of individual cardiovascular function both at rest and following certain standardized forms of stress, among them anoxemia and exercise. Since these stress tests were originally standardized from the viewpoint of studying heart disease, certain changes or refinements in method and additional observations have been necessary to establish the significance of variations in response within the normal range. The effect of the stress of anoxemia has already been described (4). This report deals with the effect of exercise.

Although exercise has long been used as a form of circulatory stress, there are few tests available which are relatively simple and precise, yet comprehensive enough to appraise total cardiovascular function in a given individual. Many workers have dealt only with the effect of strenuous exertion on athletes (5, 6, 7, 8). Others have used variable amounts of exercise or

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fixed amounts of work regardless of age, sex or weight (9, 10, 11). The exercise test developed by Master and his associates has been the one most widely used in recent years as a clinical diagnostic aid in determining the efficiency of the myocardium and in differentiating patients with coronary insufficiency from normal subjects (12, 13, 14). The test was planned to provide a short and non-strenuous form of standardized exercise which does not strain the normal heart even temporarily. The exercise consists in repeatedly ascending and descending two steps, each 9 inches high, so that only ordinary everyday muscular activity is called into play. The maximal number of ascents which could be performed in 1½ minutes without delaying the return of blood pressure and pulse rate to normal was determined by Master and Oppenheimer in 444 normal subjects, 4 to 74 years of age and of both sexes. Using the method of smoothed medians, tables were then constructed giving the required number of ascents to be made in 1½ minutes for a given weight, age and sex. Satisfactory performance was considered to be a return of blood pressure and pulse rate to resting levels within 2 minutes after exercise; 10 points (mm. Hg or beats per minute) difference was the extreme limit permitted if the subject was to be considered normal in regard to exercise tolerance. These tables and criteria form the basis of the Master exercise test in use today. They represent an important contribution concerning the aggregate exercise tolerance of many groups of normal persons, but give no information concerning individual *differences* of behavior.

In 1942 Master and his colleagues described the effect of exercise on the electrocardiogram, using the standard number of climbs indicated in the tables just described or double that number (14). Sixty-five normal persons showed no significant changes in the electrocardiogram after the two-step exercise. In 34 instances the test was repeated with double the number of climbs, again without significant electrocardiographic change. "Significant changes" were considered to be depression of the RS-T segment more than 0.5 mm. below the P-R segment, or flattening or depression of the T wave in any lead. Such changes were frequently found after exercise in the electrocardiograms of patients with angina pectoris, most commonly in Leads I and II. In a later paper, the effects of exercise and anoxemia on the electrocardiogram were compared (15). The same criteria were used, and in addition, the following changes after exercise were considered abnormal: a negative or isoelectric T wave becoming positive, the appearance of premature beats or other more significant arrhythmia, widening of the QRS, large Q waves, prolongation of the P-R interval or heart block. Thirty-three healthy men served as controls, the single exercise test only being used. Thirty-one showed no electrocardiographic changes on their first tests; the other two, who showed T wave changes attributed to infections on their first tests, were negative on their repeat tests. The authors found close correspondence between the results of the exercise and anoxemia tests in both control and cardiac subjects. Seven of eight sub-

jects with neurocirculatory asthenia, thirteen of twenty patients with coronary artery disease and one out of seven patients with hypertension showed electrocardiographic changes after exercise.

Unterman and DeGraff, in 1948, reported the effect of exercise on the electrocardiogram, using the Master two-step test, in the diagnosis of coronary insufficiency (16). Their control series included 37 normal subjects, 31 of whom performed the single and 6 the double Master test; in reporting the results, however, these two sub-groups were not separated. It was stated that the only subject who showed 1.0 mm. depression of the RS-T segment (in Lead I), and who therefore fell outside the normal range as defined by Master had performed the double standard test. Six subjects showed no electrocardiographic change at all after exercise. The remainder showed the following minor alterations, considered physiologic: changes in direction of $P_3$ and $T_3$; changes in amplitude of R and T waves; RS-T depression of 0.5 mm. (4 instances); lowering of RS-T from +0.5 to 0 mm. (1 instance). Seven of the 37 control subjects showed a lag in the return of pulse, blood pressure or both to normal resting values.

On the basis of the findings in the control group, these authors adopted somewhat stricter criteria for a positive test:

(1) A depression of the RS-T junction of more than 1 mm. in Leads I, II, III or more than 0.75 mm. in CF IV.

(2) The conversion of an upright T wave to an isoelectric or inverted T (or the reverse) in Leads I, II or CF IV.

(3) Disturbances in rhythm such as the appearance of premature beats.

Information concerning normal subjects' performance of the double Master test is thus exceedingly sparse. However, the finding that more cardiac patients showed electrocardiographic changes following the double than the single test suggested that the double test would provide the more sensitive measure for the differentiation of individual responses in normal subjects (14, 16). Accordingly, the double Master two-step test was selected as the standard form of exercise to be used in the present study.

## METHOD

The 263 subjects were all medical students between the ages of 20 and 35 years, with a mean age of 24.3 years; 244 were men and 19 were women. This group comprises all the subjects who completed exercise tests during the first two years of the comprehensive study. All were in a state of mental and physical vigor compatible with the pursuit of the medical school curriculum. None of the subjects had clinical hypertension, coronary artery disease, or rheumatic heart disease. A very few subjects had borderline blood pressure levels or a history of rheumatic fever; they were not excluded, but were studied and will be mentioned later. Teleoroentgenograms were obtained on the entire group; the heart shadow was within normal limits in regard to size and contour in every instance. The control electrocardiograms, likewise, were never grossly abnormal.

Subjects came to the laboratory 1 to 2 hours post-prandial, and rested on a couch in the horizontal position with blood pressure cuff on the left arm. A series of determinations of pulse rate and blood pressure were made at two minute intervals until consistent resting

values were obtained over a five minute period (blood pressure stable within 4 mm., pulse rate within 4 beats per minute). At this time the control electrocardiogram (standardized so that 1 millivolt gave a 10 mm. deflection) was taken with Leads I, II, III and CF IV recorded in that order. Some of the electrocardiograms were taken with a Cambridge string galvanometer, others with a Sanborn Instomatic Cardiette. The subject was then weighed with electrodes and blood pressure cuff still in place, after which he made the required number of trips over the steps according to his age and weight. The double two-step test was performed by ascending and descending the two nine inch high steps *twice* the number of trips prescribed in Master's tables in *twice* the length of time, or exactly three minutes (14). Immediately after the completion of exercise, the subject reclined once more on the couch. The blood pressure was taken at once, followed by the electrocardiogram. The four lead tracing was completed in less than 1½ minutes following the termination of exercise. Blood pressure and pulse rate were again measured, and repeated at 1 or 2 minute intervals until they had returned to resting levels (a deviation of 4 mm. systolic pressure or 4 beats per minute from the preexercise control values were the maximum variations permitted). No further electrocardiograms were taken.

Our method, therefore, differed from most published work on the Master two-step test in the following ways:

1. *Twice* the usual number of trips over the steps were taken in *twice* the time.
2. Observations on blood pressure, pulse rate and electrocardiogram were all made with the subject *recumbent*, to facilitate comparison with the anoxemia test and other studies made in the horizontal position.
3. Blood pressure and heart rate were measured *immediately* after exercise, as well as at the end of two minutes and subsequently.
4. Aside from the control tracing, the only electrocardiogram taken was made during the period 30 to 90 seconds after exercise; many were completed by 60 or 80 seconds. Other authors have made subsequent tracings as well.

## OBSERVATIONS

A total of 310 standard exercise tests were carried out on the 263 subjects, using the double two-step technique described above. While 221 students performed the test but once, 42 subjects subsequently repeated the test on one or more occasions. Sixty-seven additional tests were carried out by the students themselves with our assistance as a class room exercise; these tests are not included in the data for general analysis, but will be alluded to in regard to the repeatability of the test.

### A. *Resting Control Values*

The frequency distribution curves of the resting control blood pressure and heart rate immediately before the exercise test are shown in Figure 1.[1] The mean values for men and for women, and for the total group are given in Table I. The mean systolic pressure of the 19 women was lower than that of the men. One subject (48M80)[2] had a resting systolic pressure of 154 and a diastolic pressure of 96, although on other occasions resting blood pressures of 134/86

[1] The pressure determinations are charted on 263 subjects, the heart rates on 259, as only that number of electrocardiograms were technically satisfactory. In all 263 subjects the radial pulse rate was also recorded.

[2] In the subject numbers, men are indicated by M, women by W.

and 124/76 were recorded. In addition, two subjects (48M25, 52M11) had systolic pressures of 142 and 144 respectively, while two other subjects (48M05,

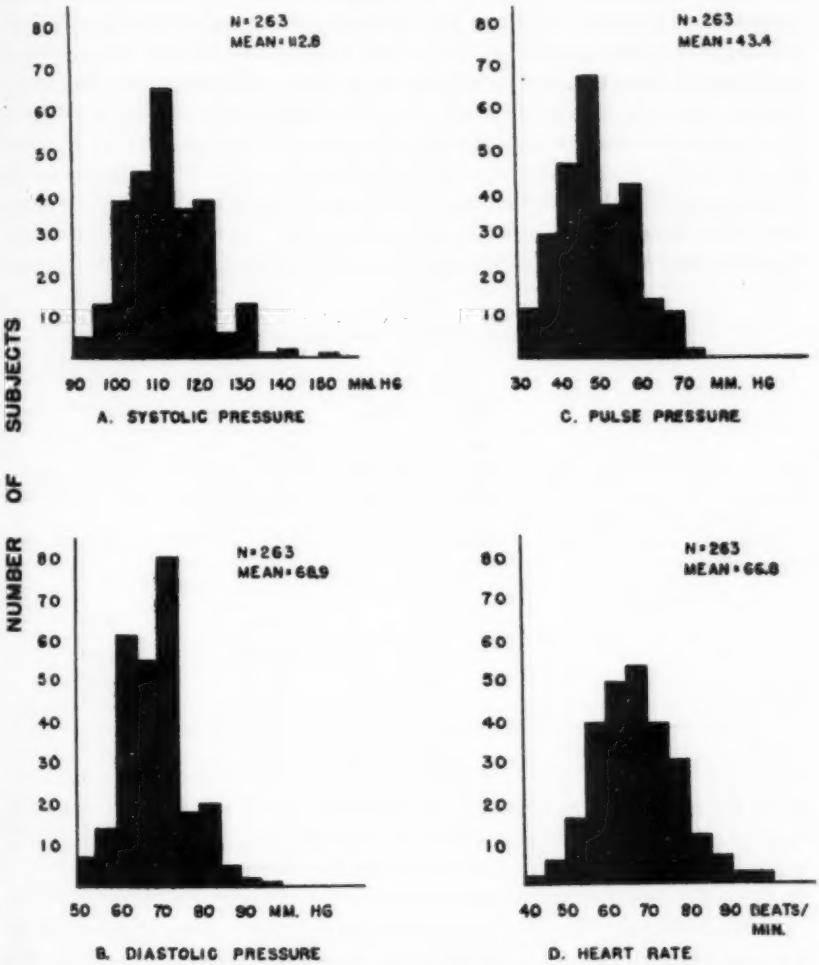



FIG. 1. The distribution curves of the resting values of systolic, diastolic and pulse pressures and of heart rate of all subjects.

51M66) had diastolic pressures of 90. In all other instances the resting blood pressure levels were under 140/90.

On account of the wide variation in electrocardiographic findings among healthy young adults, the criteria for normality have been difficult to establish (3, 17, 18). However, all of the control electrocardiograms taken on our sub-

jects fell within the range of variation which has been considered normal. The outstanding variations encountered among our subjects are listed in Table II. Aside from sinus arrhythmia, no arrhythmias were present during the control period in this group, although one subject studied subsequently (52M40) showed A-V nodal rhythm at rest which reverted to normal sinus rhythm immediately after exercise. Some degree of sinus arrhythmia was frequently present, and was sufficiently marked to be noteworthy in 72 of the subjects. The control records were interpreted with particular attention to the relationship of the RS-T segments to the isoelectric line (using the P-Q segment as the reference level) and to the direction of the T waves in each lead. It will be noted that 143 of the subjects showed elevation of the RS-T segment of at least 1 mm. in one or more leads (usually in Leads II and IV), while a smaller group showed

TABLE I

*Resting Levels of Blood Pressure and Heart Rate*

| SUBJECTS | NO. | SYSTOLIC PRESSURE | | DIASTOLIC PRESSURE | | PULSE PRESSURE | |
|---|---|---|---|---|---|---|---|
| | | Mean | Range | Mean | Range | Mean | Range |
| | | *mm.* | *mm.* | *mm.* | *mm.* | *mm.* | *mm.* |
| Men | 244 | 113.5 | 92–154 | 69.1 | 52–96 | 44.0 | 28–66 |
| Women | 19 | 103.6 | 94–132 | 67.2 | 60–82 | 37.0 | 26–64 |
| Total | 263 | 112.8 | 92–154 | 68.9 | 52–96 | 43.4 | 26–66 |

| SUBJECTS | NO. | HEART RATE | |
|---|---|---|---|
| | | Mean | Range |
| | | *beats/min.* | *beats/min.* |
| Men | 240 | 66.6 | 43–99 |
| Women | 19 | 69.0 | 54–94 |
| Total | 259 | 66.8 | 43–99 |

slight depression of RS-T, usually in Lead III. The T waves were upright in Leads I, II and CF IV in all subjects. In 18, however, the amplitude of the T waves was 1.0 mm. or less in Lead I or Lead II or both.

B. *General Characteristics of the Cardiovascular Changes Following Exercise*[3]

1. *Blood Pressure.* Definite changes in blood pressure were observed in all but one instance (48M05). Immediately after the cessation of exercise the systolic pressure consistently showed an elevation above the resting control value, with a mean increase of 30.8 mm. Hg. In general, the systolic level declined sharply from this peak, reaching the control level within five minutes. In contrast to the consistent *rise* in systolic pressure, the diastolic pressure *fell* in a majority of subjects but not in all. Thus while 54% of the entire group

[3] Based on the first tests of all but seven of the subjects; in these the second tests were used because the previous electrocardiograms were technically unsatisfactory.

showed a mean decrease in diastolic pressure of 8.4 mm., 29% showed a mean increase of 5.3 mm., while 17% of the subjects showed no change in either direction. In consequence, the pulse pressure was usually substantially increased after exercise; the mean increase was 34.1 mm., or 79% above the control value (Fig. 2 A, B and C). While a return to resting pressure levels in less than five minutes was the usual finding, 70 subjects or 26.7% failed to show such a rapid decline in systolic levels (Figure 3).

TABLE II

*The More Significant Variations Among the Control Electrocardiograms of 259 Subjects*

| ELECTROCARDIOGRAPHIC FINDING | SUBJECTS | |
|---|---|---|
| | No. | % |
| Sinus bradycardia* | 61 | 23.5 |
| Borderline A-V conduction time | | |
| P-R interval 0.20 seconds | 27 | 10.4 |
| P-R interval 0.21 seconds | 1 | 0.4 |
| Left axis deviation† | 6 | 2.3 |
| Right axis deviation† | 6 | 2.3 |
| RS-T segment elevated at least 1.0 mm. in one or more leads | 143 | 55.2 |
| in Lead I | 6 | 2.3 |
| in Lead II | 77 | 29.7 |
| in Lead III | 16 | 6.2 |
| in Lead IV | 104 | 40.2 |
| RS-T segment depressed 0.5–1.0 mm. | | |
| in Lead II only | 1 | 0.4 |
| in Lead III only | 13 | 5.0 |
| in Leads II and III | 2 | 0.8 |
| in Lead CF IV only | 2 | 0.8 |
| T wave +1.0 mm. or less in Lead I | 11 | 4.2 |
| T wave +1.0 mm. or less in Lead II | 3 | 1.2 |
| T wave +1.0 mm. or less in Leads I and II | 2 | 0.8 |
| T wave isoelectric in Lead III | 3 | 1.2 |
| T wave diphasic in Lead III | 23 | 9.0 |
| T wave inverted in Lead III | 21 | 8.2 |

* Definition of American Heart Association (19).

† Definition of Pardee (20).

2. *Heart Rate and Electrocardiogram.* It is well known that acceleration of the heart occurs following exercise. The distribution curve of the increase in heart rate recorded electrocardiographically half a minute after stair climbing is shown in Figure 2D. Increases ranging from 5 to 29 beats per minute were commonly encountered, and occurred in 69.9% of the group. However, 20.1% showed heart rates which were 30 to 64 beats per minute above the control level, while 10% showed negligible changes of from +4 to −5 beats per minute. As a rule, the heart rate steadily declined thereafter, reaching resting values within 5 minutes after the cessation of exercise. As was found with regard to

the blood pressure, the heart rate failed to return promptly to control levels in some subjects.

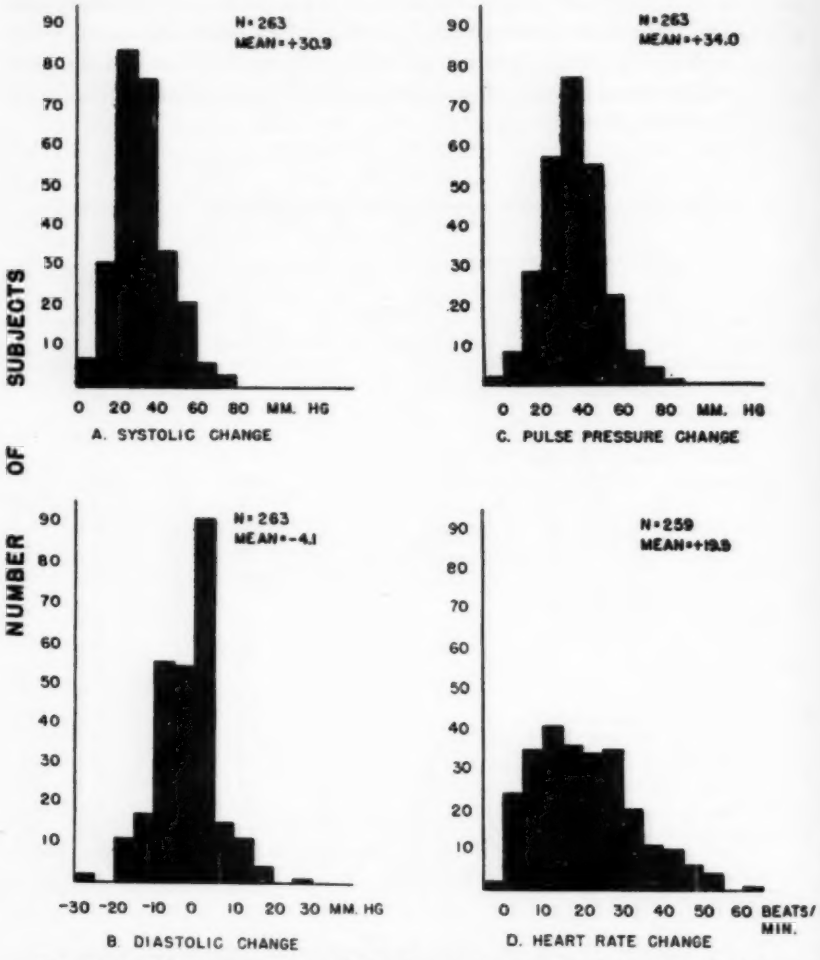



FIG. 2. The distribution curves of the change after exercise in systolic, diastolic and pulse pressures and in heart rate in all subjects. (Blood pressure changes are expressed in mm. of Hg, heart rate changes in beats/min.).

The outstanding electrocardiographic changes after exercise are summarized in Table III, and illustrated in the Appendix. These changes were distributed among 134 subjects; there were 125 subjects whose records revealed none of the changes listed. The electrocardiograms of 24 showed from three to six changes per subject, while one or two changes were observed in the records of

the other 110 subjects. Whereas 60 subjects developed heart rates of 100 to 136, in five the heart rate remained under 60. There was no general relationship between the rate at rest and the degree of acceleration after exercise. Among the 63 subjects who had resting heart rates under 60 beats per minute, 12 showed a rise in rate of less than 10 beats per minute, while 14 showed a degree of acceleration amounting to from 30 to 64 beats per minute. In the remainder, an increase of from 10 to 29 beats per minute was observed. Among the 54 subjects with the highest resting heart rates (75 to 99 beats per minute) 13

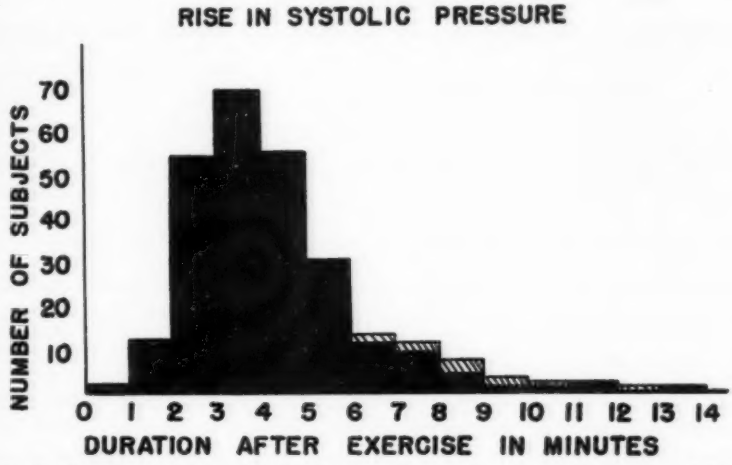



FIG. 3. Distribution curve showing the duration of rise in systolic pressure following exercise in 262 subjects.

The dark area = The minute of return of systolic pressure to within 4 mm. Hg of the control level was known in these 251 subjects.

The shaded area = The last recorded systolic pressure was more than 4 mm. Hg (usually 6 mm. Hg) above the control level, and the total duration was estimated in 11 subjects.*

* Examples:

| *Last Recorded Systolic Pressure* | *Estimated Duration* |
|---|---|
| +6 mm. at 11 min. | 12 min. |
| +12 mm. at 7 min. | 10 min. |

showed increases amounting to less than 10 beats per minute while in 17 the heart rate increased from 30 to 48 beats per minute. Auricular premature beats were noted in the tracings of six subjects,[4] while in one subject (48M33) transitory auricular tachycardia terminated early in Lead I, and in another (52M12) a brief paroxysm of auricular fibrillation was recorded in Lead CF IV. No other arrhythmias were noted.

Some lowering of T waves was noted in many records, and the T wave became

[4] 48M12, 48M60, 49M66, 49M71, 50M20, 50M29.

diphasic in one or more leads (not including Lead III) in eight subjects.[5] The T wave became isoelectric in Lead I in only one subject (49M07); such a change was not observed in Lead II or Lead CF IV. Depression of the RS-T segment below the isoelectric line of up to 1.0 mm. was observed in 41 subjects, most frequently in Lead II only. In six of these subjects, RS-T depression of 1.0 mm. or more occurred in Lead II or III or both.[6] In many instances the P-Q segment also was altered in direction after exercise, sloping downward from the end of the P wave to the beginning of the Q wave. For this reason, the use of the

TABLE III

*The Electrocardiographic Changes Occurring Immediately after Exercise Among 259 Subjects*

| ELECTROCARDIOGRAPHIC FINDING | SUBJECTS | |
|---|---|---|
| | No. | % |
| Sinus bradycardia | 5 | 1.9 |
| Sinus tachycardia | 60 | 23.2 |
| With gradual slowing | 30 | 11.6 |
| Abruptly terminated by sinus arrhythmia | 22 | 8.5 |
| With runs of rapid rhythm alternating with sinus arrhythmia | 8 | 3.1 |
| Auricular premature beats | 6 | 2.3 |
| Paroxysmal auricular tachycardia | 1 | 0.4 |
| Paroxysmal auricular fibrillation | 1 | 0.4 |
| $T_1$ +1.0 mm. or less | 48 | 18.5 |
| $T_2$ +1.0 mm. or less | 9 | 3.5 |
| $T_1$ diphasic | 2 | 0.8 |
| $T_1$ isoelectric | 1 | 0.4 |
| $T_2$ diphasic | 7 | 2.7 |
| $T_3$ changed in direction or contour | 40 | 15.4 |
| $T_{aF}$ diphasic | 1 | 0.4 |
| RS-T segment depressed below the isoelectric line | | |
| Lead I up to 1.0 mm. | 2 | 0.8 |
| Lead II up to 1.0 mm. | 27 | 10.4 |
| 1.0 mm. or more | 5 | 1.9 |
| Lead III up to 1.0 mm. | 7 | 2.7 |
| 1.0 mm. or more | 3 | 1.2 |
| Lead IV up to 1.0 mm. | 4 | 1.5 |

P-Q segment as a reference level was not entirely satisfactory, since it was not necessarily isoelectric. It was, however, preferable to the T-P segment, which during sinus tachycardia frequently remained elevated. We therefore selected the junction of the downward limb of the P wave with the P-Q segment as our point of reference in instances where the P-Q segment was not level. Using this reference point, six subjects appeared to show an RS-T depression of slightly more than 1.0 mm. after exercise. However, if the mid-

[5] (48W03 I; 48M17 I and II; 48M19 II; 49W37 II and CF IV; 50M26 II; 50M37 II; 50W68 II; 52M12 II).

[6] See Table VIII.

point or terminal point of the P-Q segment were chosen, the relative depression of RS-T would be nearer 1.0 mm. (See Appendix.)

3. *Symptoms.* This amount of exercise produced no untoward symptoms in any of the subjects. There was no instance of precordial pain or discomfort. Some subjects breathed a little heavily for as much as a minute after lying down, but dyspnoea was never conspicuous. The subjects performed the test in a matter-of-fact way, and never seemed to become tense or disturbed.

### C. *Further Observations Concerning the Significance of the Cardiovascular Response to Exercise*

1. *Duplicate Tests.* The question will be raised as to the repeatability of these results. Exercise tolerance tests, like other types of biological data, are subject to a certain amount of variation, since the conditions of the test and the state of the individual can never be precisely the same on any two occasions. This intraindividual variation has been analyzed in detail by others, notably

TABLE IV

| IMMEDIATELY AFTER EXERCISE: | TEST 1 | TEST 2 | TEST 3 | IN CLASS* |
|---|---|---|---|---|
| Pulse Pressure Change (mm. Hg.)..... | +26 | +30 | +28 | +40 |
| Heart Rate Change (beats per minute)... | +18 | +18 | +12 | +16 |

* Observations made by fellow students.

by Simonson, Brozek and Keys in regard to the electrocardiogram (21) and by Duncan, Stevenson and Wolff in regard to other physiological measurements before and after exercise (22). In the present study, dealing with a large number of subjects, the first test was usually the only test. We have, therefore, endeavored to concentrate upon the broad aspects which seem likely to indicate fundamental individual differences, and to avoid emphasis upon details that may be affected by day to day variations, which are usually relatively small in healthy subjects (22).

We have certain data which throw light on the question of the repeatability of the test. First, there are individuals in whom the test is almost precisely the same on a number of trials. For example, Subject 51M22 who, during the period of one year, performed three double exercise tests under laboratory conditions and a fourth test as a class room exercise, showed the following changes, which were independently recorded: (see Table IV)

This subject was not selected for stability of circulatory response, but was the only subject who by chance underwent this number of tests. The three tests were performed by two different technicians.

Secondly, the mean changes shown by the nine subjects who had two complete double exercise tests were very similar (see Table V). While most of the individual tests were similar, they were occasionally quite different. In general, the pulse pressure changes were more consistent than the heart rate changes.

Finally, observations of the blood pressure changes after exercise were repeated under laboratory conditions on 45 volunteers who were otherwise unselected; repetition of the electrocardiograms was omitted. The mean pulse pressure for each pair of tests was then calculated. In 36, or 80%, the observed pulse pressures differed from the mean pulse pressure by from 0 to 9 mm., with an average difference of ±4.5 mm. The other 9 subjects showed greater inconsistency. The mean pulse pressure increase after exercise in these 45 subjects was +33.1 mm. on the first test and +38.4 mm. on the second test, indicating the absence of any training effect in the direction of smaller responsiveness. Interestingly enough, 30 subjects who underwent double exercise tests as a physiology class exercise under our supervision showed a mean rise in pulse pressure of +34.3 mm. in the classroom and of +35.6 mm. in our laboratory. The altered conditions did not in this instance, therefore, produce any overall difference in the behavior of the blood pressure.

TABLE V

| IMMEDIATELY AFTER EXERCISE: | TEST 1 | TEST 2 |
|---|---|---|
| Mean Pulse Pressure Change (mm. Hg.) | +43.8 | +42.0 |
| Mean Heart Rate Change (beats per minute) | +27.3 | +30.7 |

2. *The Relationship of Athletic Training to the Response Following the Exercise Test.* Much has been written concerning the role of athletic training in modifying patterns of circulatory reactivity (23, 24, 25). Although we have not made direct observations concerning the effect of various degrees of training upon individual subjects, we know that at the time of the test none of our subjects were at the peak of physical condition such as results from daily strenuous exercise. All exercise tests were carried out during the academic year while the subjects were fully occupied with their medical studies. No tests were performed within two weeks of starting medical school in the fall, and only 6% of the tests were performed during the latter part of the first month of academic work.

The subjects were questioned concerning the types and amounts of exercise taken during the month preceeding the tests. Over half had taken no exercise whatever during that period, and nearly one-third more had exercised but little (e.g. horseback riding, occasional golf, ping pong). Only 12% had exercised vigorously two or three times a week during the month preceeding the test (e.g. basketball, running, tennis, football, handball, badminton). Detailed athletic histories concerning ability and degree of participation in sports before coming to medical school were also obtained. On the basis of this information, it has been possible to select those who were non-athletic as well as those who prior to medical school were moderately athletic (e.g. participation in some of

the usual college sports in season) or outstanding athletes (e.g. varsity football, track or crew; amateur state tennis champion).

The response to exercise of four groups of subjects who could be clearly characterized in regard to different degrees of athletic ability and training has been analyzed in Table VI. It will be observed that there were individuals in every group who responded to exercise with marked changes in pulse pressure and in heart rate. The type of circulatory response to exercise did not seem to be closely correlated with the history of athletic participation either in previous years or immediately before the test, except for the fact that the heart rate of those who had never been athletic showed a greater mean rise following exertion than was observed in the other three groups.

TABLE VI

*The Relationship of Athletic Training to the Circulatory Response to Exercise*

| AMOUNT OF EXERCISE | | NO. OF SUBJECTS | PULSE PRESSURE CHANGE MM.HG | | HEART RATE CHANGE BEATS/MIN. | |
|---|---|---|---|---|---|---|
| Before Medical School | One Month Before Test | | Mean | Range | Mean | Range |
| Non-athletic..... | None | 17 | +34.2 | −4 to +60 | +29.6 | +11 to +51 |
| Moderately athletic..... | Moderate | 39 | +32.7 | +6 to +66 | +19.9 | +4 to +46 |
| Outstanding athlete..... | None | 14 | +35.2 | +18 to +64 | +20.6 | +1 to +46 |
| Outstanding athlete..... | Vigorous | 20 | +31.3 | +12 to +56 | +17.3 | +3 to +41 |

3. *Relationship of the Control Levels of Blood Pressure or Heart Rate to the Degree of Response to Exercise.* When the subjects were arranged in groups according to the resting levels of systolic pressure, diastolic pressure or heart rate, no significant differences in response to exercise were found between the groups (Table VII A, B, and C). Only in regard to systolic pressure did a tendency toward increased lability following exercise exist among the subjects with the highest resting systolic levels. Although the differences were not great enough to be statistically significant, slight progressive diminution in systolic lability after exercise occurred among the groups with consecutively lower systolic pressures until the group with resting values of 105–109 mm. was reached; this group showed the smallest mean and median rises in systolic pressure following exercise. It is noteworthy that the subjects with the lowest systolic levels at rest were again more reactive, and in this way resembled those with high resting systolic levels.

4. *The Duration of the Circulatory Response to Exercise.* A prolongation of the circulatory response to exercise has been considered to be of clinical importance. The single two-step test was originally devised in such a way that the criterion for its satisfactory performance was a return of systolic pressure and of pulse rate to pre-exercise levels within two minutes after the end of exercise (12). If the return to resting values was delayed, myocardial insufficiency was said

to be present (13). Exceptions to this idea have gradually appeared in the literature. Unterman and DeGraff noted a delay in the return of pulse, blood pressure or both to resting levels in seven of 37 normal subjects (16). Subjects with neurocirculatory asthenia or anxiety were also reported to show such delays in the absence of myocardial insufficiency (13, 22).

TABLE VII

*Relationship of Resting Levels of Blood Pressure or Heart Rate to the Degree of Change Following Exercise*

| RESTING VALUES | SUBJECTS | | CHANGE FOLLOWING EXERCISE | | |
|---|---|---|---|---|---|
| | No. | % | Mean | Median | Range |
| A. Systolic Pressure (mm.) | | | | | |
| 130 and over | 17 | 6.5 | +37.2 | +36.0 | +10 to +76 |
| 125–129 | 6 | 2.3 | +33.3 | +33.0 | +18 to +50 |
| 120–124 | 38 | 14.5 | +32.7 | +31.0 | +2 to +61 |
| 115–119 | 36 | 13.7 | +33.7 | +32.0 | +6 to +69 |
| 110–114 | 65 | 24.7 | +30.3 | +30.0 | −2 to +70 |
| 105–109 | 45 | 17.1 | +29.0 | +26.0 | +6 to +58 |
| 100–104 | 38 | 14.5 | +29.3 | +29.0 | +8 to +50 |
| 99 and under | 18 | 6.8 | +33.4 | +33.0 | +20 to +56 |
| Total | 263 | | +31.5 | | −2 to +76 |
| B. Diastolic Pressure (mm.) | | | | | |
| 90–99 | 3 | 1.1 | −8.0 | −6.0 | −18 to 0 |
| 80–89 | 26 | 9.9 | −3.0 | −1.0 | −26 to +26 |
| 70–79 | 97 | 36.9 | −3.1 | −2.0 | −24 to +16 |
| 60–69 | 116 | 44.1 | −2.1 | −1.0 | −28 to +18 |
| 50–59 | 21 | 8.0 | −3.5 | −1.0 | −54 to +14 |
| Total | 263 | | −2.7 | | −54 to +26 |
| C. Heart Rate (Beats/Min.) | | | | | |
| 80 and over | 25 | 9.7 | +20.9 | +21.0 | 0 to +42 |
| 70–79 | 69 | 26.6 | +19.6 | +19.0 | −3 to +48 |
| 60–69 | 102 | 39.4 | +19.0 | +17.0 | 0 to +51 |
| 59 and under | 63 | 24.3 | +21.2 | +20.0 | +3 to +64 |
| Total | 259 | | +19.8 | | −3 to +64 |

The usual duration of the circulatory response to the double exercise test has not been described. Following three minutes of step climbing, the systolic pressure of our subjects most frequently returned to within 4 mm. of resting values during the fourth minute, as shown in Fig. 3. This return was delayed until the seventh minute or later in 40 of our subjects, however. Duplicate tests were performed under laboratory conditions on six subjects whose systolic pressures reached control levels seven to eleven minutes after exercise. On

the second test a delayed type of response was again evident in all six subjects.[7] None had reached control levels at the end of four minutes, and lags of as much as eight minutes were recorded.

No single reason for such a comparative delay in the return of the circulation of healthy subjects to the resting state is readily apparent. The group of 40 subjects included athletes and non-athletes, those in good physical condition and those out of training, some with excellent nervous stability and some who were unstable, some who showed increased circulatory responsiveness in other ways, and some who did not. Parental cardiovascular disease was present in this group in about the same proportion as in the total population. The subjects were free from infection and were not thought unusually tense at the time of their tests, nor did they complain of any symptoms. It seems probable from the shape of the distribution curve in Figure 3 that delays in return to resting values up to 9 or 10 minutes are characteristic of certain healthy individuals, and should not be regarded as an indication of myocardial insufficiency or of neurocirculatory asthenia, although delay may be more likely to occur in individuals with such disorders.

5. *Electrocardiographic Changes.* Although the primary purpose of this study has been to describe the circulatory changes which occur following the double Master exercise test, rather than to establish criteria for normality, certain pertinent observations may be mentioned. It will be observed that most if not all of the criteria for a positive exercise test as defined by Unterman and DeGraff (16) were fulfilled by a few of our subjects (Table III and Appendix). In view of the fact that the criteria of Unterman and DeGraff were primarily based on the *single* Master exercise test, our findings following the *double* test are *not* necessarily abnormal, but they should be considered as borderline or doubtful. We cannot state with certainty at present whether or not they are significant in terms of past or future cardiovascular disease. arrhythmias or T wave changes after exercise gave histories of acute rheumatic fever. They were Subject 52M12, who developed diphasic T waves in Lead II and paroxysmal auricular fibrillation briefly in Lead CF IV, and Subject 49M07, the only one whose T waves became isoelectric in Lead I. Moreover, Subject 49W37, who developed diphasic T waves in Leads II and CF IV, gave a history of diphtheria, repeated otitis media, mastoidectomy and pneumonia, all occurring in childhood. While these three subjects were all free from any clinical or roentgenological evidence of heart disease, the possibility of residual myocardial scarring certainly exists.

Depression of the RS-T segment below the isoelectric line, on the other hand, was not associated with a history of rheumatic fever. The fact that quite a number of subjects show RS-T depression approaching 1.0 mm. suggests that this response is largely a physiologic one. The circulatory responses of the six

[7] 48M74, 51M07, 51M08, 51M35, 51M54, 51M64.

Two of the subjects with the most unusual findings among those with

subjects who showed depression of the RS-T segment of 1.0 mm. or more are given in Table VIII. It will be observed that, in comparison to the other two groups of subjects showing marked electrocardiographic changes, and in contrast to the findings for the total population, cardiovascular responsiveness was greater, and the mean resting values, especially for systolic pressure, were definitely higher. While all of the six subjects with the most pronounced RS-T

TABLE VIII

*The Blood Pressures and Heart Rates of Six Subjects with Marked RS-T Depression after Exercise Compared with Two Groups Showing Other Electrocardiographic Changes, and with the Total Population*

| SUBJECT NO. | NO. OF SUBJECTS | SYSTOLIC B. P. (MM.) | | | DIASTOLIC B. P. (MM.) | | | PULSE PRESSURE (MM.) | | | HEART RATE (BEATS/MIN.) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Control | Change | Maximum | Control | Change | Maximum | Control | Change | Maximum | Control | Change | Maximum |
| RS-T depressed more than 1.0 mm. | | | | | | | | | | | | | |
| 48M19.. | | 110 | +70 | 180 | 64 | −14 | 50 | 46 | +84 | 130 | 73 | +27 | 100 |
| 48M21.. | | 116 | +34 | 150 | 72 | +8 | 80 | 44 | +26 | 70 | 77 | +48 | 125 |
| 48M25.. | | 142 | +38 | 180 | 84 | +6 | 90 | 58 | +32 | 90 | 59 | +52 | 111 |
| 48M32.. | | 126 | +40 | 166 | 68 | +2 | 70 | 58 | +38 | 96 | 71 | +32 | 103 |
| 48M39.. | | 112 | +42 | 154 | 68 | +6 | 74 | 44 | +36 | 80 | 79 | +28 | 107 |
| 48M43.. | | 134 | +34 | 168 | 86 | −6 | 80 | 48 | +40 | 88 | 70 | +33 | 103 |
| Mean... | 6 | 123.3 | +43.0 | 166.3 | 73.7 | +0.3 | 74.0 | 49.7 | +42.7 | 92.3 | 71.5 | +36.7 | 108.2 |
| T Wave Changes[a] | | | | | | | | | | | | | |
| Mean... | 9[b] | 113.3 | +33.1 | 146.4 | 67.7 | −3.3 | 64.4 | 45.6 | +36.4 | 82.0 | 75.7 | +22.2 | 97.9 |
| Arrthymias | | | | | | | | | | | | | |
| Mean... | 8[c] | 111.5 | +33.5 | 145.0 | 62.8 | −4.6 | 58.1 | 47.3 | +34.6 | 81.9 | 70.3 | +27.1 | 97.4 |
| Total Population | | | | | | | | | | | | | |
| Mean... | 263[d] | 112.8 | +30.9 | 143.7 | 68.9 | −4.1 | 66.2 | 43.4 | +34.0 | 77.5 | 66.8 | +19.9 | 86.7 |

[a] T waves isoelectric or diphasic in Leads I, II or CF IV after exercise.
[b] One subject (48M19) also included in the six with RS-T depressions.
[c] One subject (52M12) also included in the ten with T wave changes.
[d] Total population for heart rate = 259.

depression developed sinus tachycardia following exercise, it was only marked in one instance. Moreover, among the other 54 subjects with sinus tachycardia following exercise, 44 showed no significant depression of the RS-T segments, so that a simple relationship between tachycardia and RS-T segment depression cannot be said to exist. The subjects with the most pronounced RS-T depression were unusual in several different ways. Thus Subjects 48M45 and 48M43 had unusually high resting blood pressures, while Subject 48M19 showed the greatest individual increase in pulse pressure following exercise in

the entire study. In addition, Subject 48M25 showed a tremendous increase in heart rate from sinus bradycardia to sinus tachycardia although the maximal heart rate of 111 was not conspicuously high. These findings taken together suggest that in young adults, the RS-T depression following exertion is not directly proportional to the maximal heart rate, but may be related to some more comprehensive hemodynamic change.

6. *Interrelationship of Changes in Pulse Pressure and Heart Rate after Exercise.* The marked variability in the individual response to exercise of both blood pressure and heart rate has been clearly illustrated in Figure 2. In order to determine whether a general relationship existed between the degree of change in blood pressure and the degree of acceleration of the heart, the change in pulse pressure in each individual was plotted against the increase in heart rate in the same subject (Fig. 4). It may be seen at a glance that no significant positive correlation which is applicable to the entire group of subjects exists between the two variables. Some individuals showed great increases in heart rate with little change in blood pressure following exercise, while others responded chiefly by a great increase in pulse pressure. A small percentage showed little change in either heart rate or blood pressure, in contrast to another small group which responded with excessive rises in *both* pulse pressure and heart rate. Thus a number of types of cardiovascular response to exercise were differentiated by the simultaneous analysis of the changes in pulse pressure and heart rate.

In order to establish a simple distribution grid for the appraisal of individual cardiovascular responsiveness to exercise, the scatter diagram of the responses of our entire unselected population shown in Figure 4 was divided into nine areas by demarcating the boundaries of the first and fourth quartiles of each of the two variables. Those boundaries are shown in Figure 5, together with the percentage of the 259 subjects lying in each area; a Roman numeral has been assigned to each area for ready reference. Fifteen, or 6% of the subjects fell in Area III, the "Area of Hyperreactivity". In this group, the double Master exercise test produced increases in pulse pressure of from 42 to 84 mm., and in heart rate of from 28 to 64 beats per minute. Since circulatory lability has been thought to characterize prehypertensive and young hypertensive individuals, it was of interest to determine whether these subjects also showed other traits which have been associated with an increased susceptibility to future cardiovascular disease.

The fifteen subjects in Area III were therefore compared with the total population of subjects both in regard to the incidence of positive parental history and of six physiologic characteristics which have been described as showing such an association (26–33). These characteristics together with their definitions in the present study are as follows:

1. *Overweight.* 20 or more pounds overweight, according to the tables of the

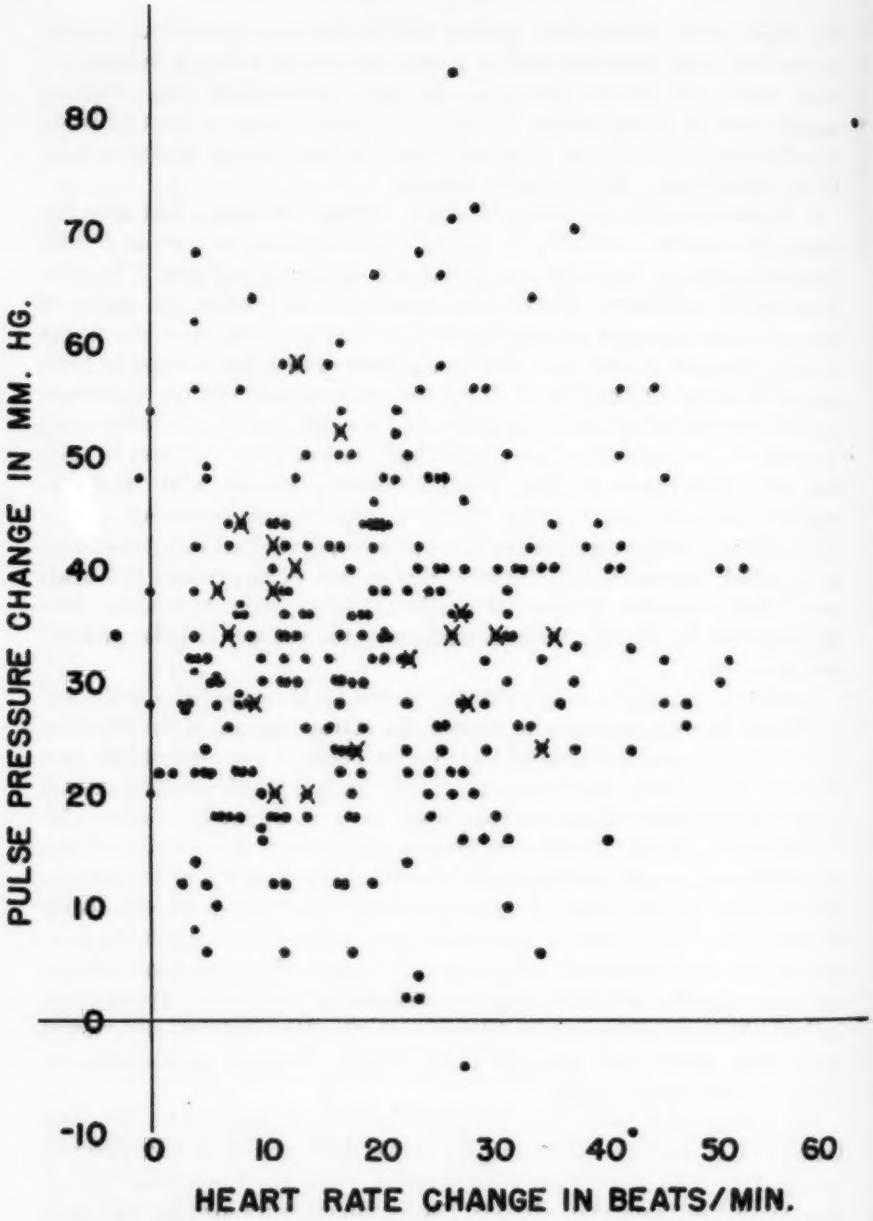



FIG. 4. Relationship of increase in pulse pressure to increase in heart rate immediately after exercise among 259 students. Each dot represents one subject. Women are indicated by Xs.

Association of Life Insurance Directors and Actuarial Society of America, 1912.

2. *High Resting Blood Pressure.* A pressure of 120 mm. or more systolic and/or 80 mm. or more diastolic, at the end of the control period immediately before exercise.

3. *Transitory Hypertension.* A pressure of 150 mm. or more systolic and/or 90 mm. or more diastolic recorded on at least one occasion during casual or control blood pressure determinations, followed by lower levels on the same or other days.

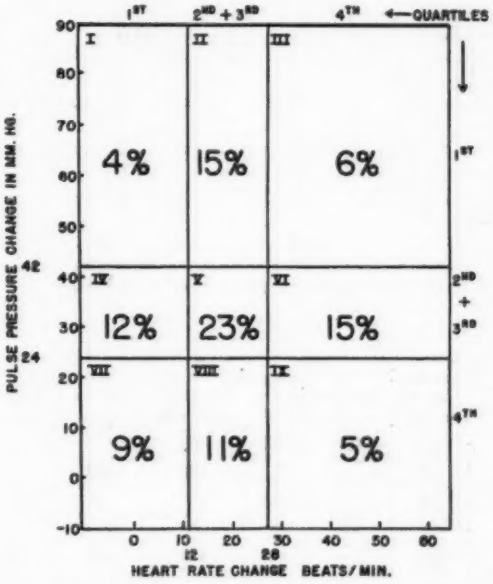



FIG. 5. Relationship of increase in pulse pressure to increase in heart rate immediately after exercise among 259 students. Percentages indicate distribution of total population by quartiles.

4. *High Resting Heart Rate.* A heart rate of 80 beats per minute or over obtained from the control electrocardiogram.

5. *Transitory Tachycardia.* A pulse rate of 100 beats per minute or over obtained on at least one occasion during casual or control determinations, followed by slower rates on the same or other days.

6. *Positive Cold Pressor Test.* A systolic and/or diastolic rise of 20 mm. or more during or immediately after immersion of the hand and wrist in icewater at 4°C. for one minute.

The results of such a comparison are given in Table IX; they indicate that the incidence of positive parental history and of each of the six characteristics defined above is considerably greater among the 15 subjects in Area III than

TABLE IX

*Characteristics of 15 Subjects Showing Circulatory Hyperreactivity to Exercise Compared with 257 Unselected Subjects*

| | 15 HYPERREACTIVE SUBJECTS (AREA III) % | 257* UNSELECTED SUBJECTS % |
|---|---|---|
| Positive parental history of hypertension and/or coronary artery disease | 53.3 (61.5)† | 23.0 (31.6)† |
| Overweight | 33.3 | 12.1 |
| High resting blood pressure | 60.0 | 26.1 |
| Transitory hypertension | 46.6 | 12.5 |
| High resting heart rate | 33.3 | 10.1 |
| Transitory tachycardia | 20.0 | 11.7 |
| Hyperreactivity to cold | 33.3 | 20.2 |

* 257 of the 263 subjects in the present study had complete data including cold pressor tests.
† Percentages calculated with unknown parental histories excluded.

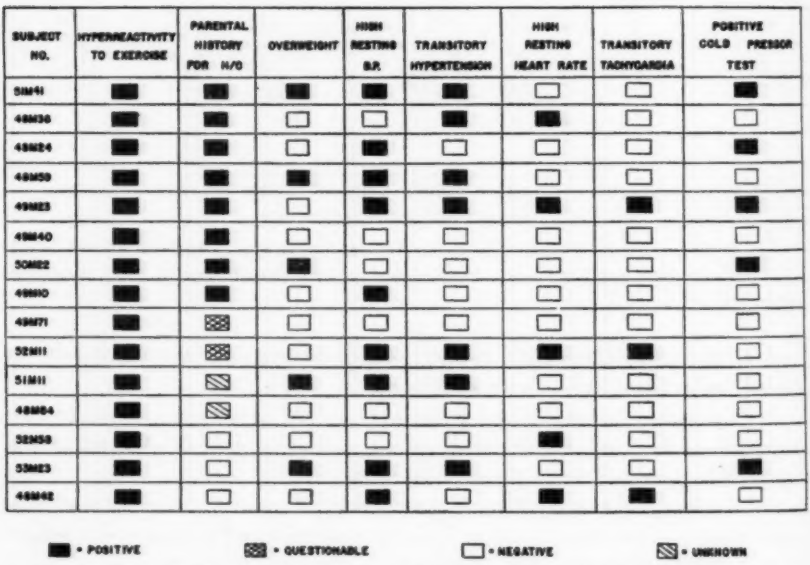



FIG. 6. The individual characteristics of the fifteen subjects with circulatory hyperreactivity to exercise. (Characteristics are defined in the text.)

in the total unselected population. In most instances the difference in the frequency of a given trait between the two groups was at least two or threefold.

An analysis of the distribution of these characteristics among the individual subjects of Area III is shown in Figure 6. Two thirds of the subjects were positive for from three to six of the factors listed. Particularly striking was the occurrence of a positive parental history in eight subjects, while in two more subjects the parental history was questionably positive, and in two it was unknown. Of the eight students with a positive parental history, all but one told of a parent who had suffered from a serious form of cardiovascular disease as indicated by death, a stroke or coronary occlusion. The positive parental histories, several of which illustrate the combined occurrence of hypertension and coronary artery disease, are as follows:

*51M41.* Father. Angina pectoris at 54, died of myocardial infarction at 56.

*48M36.* Father. Angina pectoris, atypical, at 40. Typical at 49. Myocardial infarction at 54. Mild hypertension.

*48M24.* Father. Hypertension discovered at 46. Died of malignant hypertension at 49.

*48M59.* Father. Myocardial infarction at 51. Hypertension.

*49M23.* Mother. Hypertension discovered at 39. Myocardial infarction at 43 and 45. Sympathectomy at 48. Died in congestive heart failure at 52.

*49M40.* Father. Myocardial infarction at 52.

*50M22.* Mother. Hypertension discovered at 51. Stroke at 56. (Father died of "nephritis" at 34.)

*49M10.* Mother. Hypertension discovered at 50. B.P. 195/100 at 58.

The questionable parental histories were:

*52M11.* Mother. Blood pressure "high" when examined for a job at 41; "always rises when examined". Taken at home B.P. 144–124/70.

Father. Two attacks of "heart cramps" following heavy lifting at 41. The diagnosis of coronary artery disease was considered, but an electrocardiogram was negative.

*49M71.* Father. Died of "dropsy" at 50 after a brief illness. Other circumstances unknown except that heart disease had not been recognized in previous years.

Thus in this group of parents cardiovascular disease was first suspected or recognized between the ages of 39 and 54 years, and was usually rather rapidly progressive as well as severe.

The close correlation between positive parental history and hyperreactivity to exercise may be demonstrated in another way. Eliminating subjects with questionable or unknown parental histories, the circulatory response to exercise of 64 subjects with definite parental hypertension and/or coronary

disease, (HC Group), and of 98 subjects with negative parental history, (N Group), were plotted on the distribution grid shown in Figure 5. If the genetic makeup of the individual as indicated by his parental history were entirely

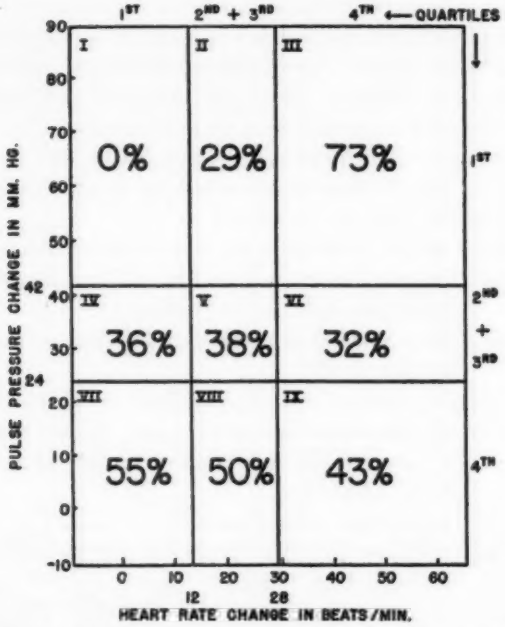



FIG. 7. Relationship of circulatory lability after exercise to parental history of hypertension and/or coronary disease.

A comparison of the immediate response of pulse pressure and heart rate to exercise of 64 subjects with positive parental history for hypertension and/or coronary artery disease and of 98 subjects with parental history negative for hypertension, coronary disease, obesity and diabetes. The percentages indicate the proportion of the subjects in each area with positive parental history.

*Composition of Population Charted*

| PARENTAL HISTORY FOR H AND/OR C | | | | | |
|---|---|---|---|---|---|
| Positive | | Negative | | Total | |
| No. | % | No. | % | No. | % |
| 64 | 39 | 98 | 61 | 162 | 100 |

unrelated to his circulatory response to exercise, then by random distribution 39% of the population in each of the nine areas should come from the HC Group, and the remainder from the N Group. Actually, however, eight out of eleven, or 73% of the individuals in Area III, the Area of Hyperreactivity,

had a history of parental hypertension and/or coronary disease, strongly suggesting that their circulatory lability is on a constitutional basis (Figure 7). In contrast, when a synthetic population composed of 38 subjects with a history of parental obesity and/or diabetes without hypertension or coronary

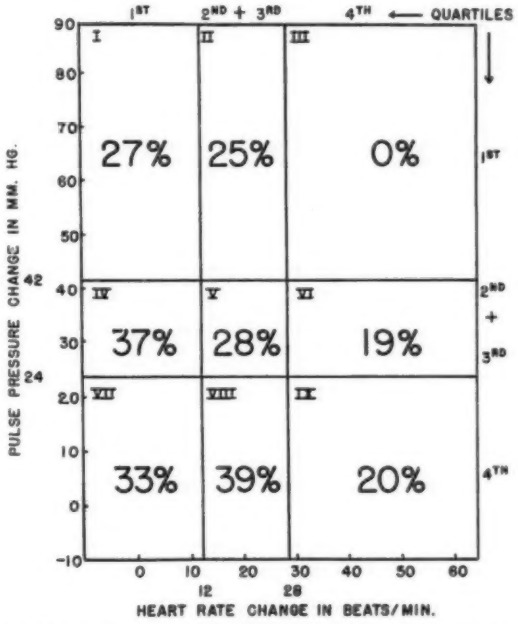



FIG. 8. Relationship of circulatory lability after exercise to parental history of obesity and/or diabetes.

A comparison of the immediate response of pulse pressure and heart rate to exercise of 38 subjects with positive parental history of obesity and/or diabetes and of 98 subjects with parental history negative for hypertension, coronary disease, obesity and diabetes. The percentages indicate the proportion of the subjects in each area with positive parental history.

*Composition of Population Charted*

| PARENTAL HISTORY OF O AND/OR D | | | | | |
|---|---|---|---|---|---|
| Positive | | Negative | | Total | |
| No. | % | No. | % | No. | % |
| 38 | 28 | 98 | 72 | 136 | 100 |

disease (OD Group) were mixed with the 98 subjects with negative parental history (N Group), none of the subjects with obese or diabetic parents had responses which fell in the Area of Hyperreactivity (Fig. 8). Instead, they tend to be grouped in the Areas of Hyporeactivity, as were some subjects in

the HC Group (Fig. 7). While the number of subjects falling in these areas is too small to permit definite conclusions in regard to the ultimate significance of these findings, they certainly suggest that hereditary patterns play an important role in determining the physiologic responses of the individual to stress, and that possibly both hyperreactivity and hyporeactivity to exercise are associated with different forms of parental disease.

## DISCUSSION

Our studies clearly demonstrate the remarkable variability of the individual circulatory response of healthy young adults to a simple form of stress. They re-emphasize the necessity for careful study of the responses of a large number of subjects before the establishment of criteria for abnormal responses. Although such criteria have been described for the Master two-step test, the groups of normal subjects heretofore studied have been small and especially so for any given age group. Moreover, no clear distinction has been drawn between the normal response to the single and to the double Master two-step test. This is a necessary consideration, since it has recently been shown that in general the cardiovascular and electrocardiographic changes observed in normal subjects increase in proportion to the severity of the circulatory stress. (4, 34)

The resting control values for blood pressure and heart rate obtained in the present study were very similar to those of other workers. (25, 18) Among 265 Harvard undergraduate students, aged 17 to 22 years, Brouha and Heath found the mean recumbent systolic pressure to be 115 mm., compared to a mean of 113.5 mm. for our male subjects (Table I). The systolic range of the Harvard group was from 95 to 145 mm., with levels above 140 mm. recorded in five of their subjects. Their mean recumbent pulse rate of 66 beats per minute, with a range of 40 to 100, was almost identical to ours. Although Graybiel, Gates and Webster found the slightly lower mean heart rate of 63.8 among 1000 young healthy aviators in training at a mean age of 23.7 years, their distribution curve of heart rates and ours are almost identical in contour. Such an agreement of findings in three independent studies of normal young men, as exemplified by Harvard undergraduates, aviation cadets and Johns Hopkins medical students, indicates that these basic physiologic characteristics are consistent and have been determined with accuracy, and suggests that in general our data may be considered as representative for healthy young adults.

The distribution grid described in this paper provides a simple way of differentiating subjects according to patterns of cardiovascular response to exercise, since the changes in systolic pressure, diastolic pressure and heart rate are all represented in a single graphic expression. Such a grid systematizes the different patterns of response and delineates basic groups for purposes of comparison and cross-correlation. Through its use, as the total number of subjects studied increases, the interrelationship of some of the electrocardiographic and circulatory changes following exercise may be further clarified. As an indication

of this possibility, it is of interest that five of the six subjects with the greatest R-ST depression following exercise (Table VIII) showed patterns lying in Area VI, although only 15% of the total population fell in this area (Fig. 5). At present we are unable to interpret isolated electrocardiographic findings falling outside of the accepted normal limits.

Our studies give support to the concept that individual hemodynamic patterns appearing in response to circulatory stress are just as distinctive as the physiologic characteristics observed under resting conditions, and may be of greater significance in terms of future cardiovascular disease. Evidence is accumulating that many indications of circulatory lability are present long before the appearance of elevated blood pressure or other clinical signs of hypertension. Thus O'Hare, Walker and Vickers in 1924 first pointed out that most hypertensive patients were aware of certain manifestations of vasomotor instability as early as the second decade of life (35). Ayman made further observations in regard to the hyperreactive emotional and physical responses of hypertensive patients, and again emphasized the fact that these hyperactive responses were life long characteristics (36). Hines and Brown devised the cold pressor test for the purpose of measuring the degree of vasomotor reactivity produced by a standardized stimulus (32). Hypertensive patients were found to show excessive rises in blood pressure in response to the cold stimulus, and 18.7 % of 400 school children were also "positive hyperreactors" to the test. Inasmuch as every child in that study who was a positive hyperreactor was found to have one parent who either had hypertension or was likewise a positive hyperreactor, Hines postulated that the trait was inherited as a dominant characteristic (37). A significant rise in blood pressure following the standard cold stimulus was thought to indicate increased vasoconstriction or vasomotor hyperreactivity and to bring out "latent hypertension". Emotional stimulation, often resulting in elevation of the systolic pressure alone, was attributed to "cardiac stimulation" rather than to vasoconstriction, and was thought to be of questionable significance as an index of "latent hypertension". However, new importance has been given to the prognostic significance of cardiac overactivity to stimuli by the observations of Levy, White, Stroud and Hillman (31). Not only transitory hypertension but transitory tachycardia was found by them to show a positive correlation with subsequent cardiovascular disease, and this relationship was even more striking when both traits were present in the same individual.

Through our simultaneous analysis of the changes in blood pressure and heart rate resulting from exercise, we have been able to identify a group of subjects who exhibit circulatory hyperreactivity of a different type than that produced by a cold stimulus. The unusually high incidence of parental history of cardiovascular disease among these subjects suggests that hyperreactivity to exercise may bear a relationship to future cardiovascular disease in certain instances. While follow-up studies are necessary before the significance of the circulatory

response to exercise as measured by our distribution grid is fully understood, it may provide a way for bringing into better focus the concept of general circulatory hyperreactivity.

The prognostic significance of circulatory hyporeactivity to various forms of stress has yet to be determined. Starr showed that subjects with ballistocardiograms which were abnormally small in amplitude developed heart disease in large numbers during the decade following the taking of the ballistic record (38). These subjects were at rest, however, and the finding is probably more closely related to insidious myocardial damage already present than to the physiologic characteristics of the individual preceding the development of coronary artery disease. Preliminary studies on the effect of oximeter-controlled anoxemia upon the cardiac output of healthy young adults as determined by the ballistocardiographic method indicate that there is a wide range in the degree of responsiveness to the same anoxemic stimulus (39). Among thirteen subjects studied at 70% arterial saturation, the increase in cardiac output above that observed at rest ranged from +20.4% to +84.9%. Thus we are able to distinguish both hypo- and hyperreactive subjects by this method, as well. Studies are in progress to determine the interrelationship of the two forms of stress, which produce somewhat different circulatory responses.

## SUMMARY

1. The patterns of cardiovascular response to standardized exercise of 263 healthy young adults have been studied, using the double Master two-step test.

2. The degree, range and duration of the circulatory changes immediately after such standardized exercise are described for the first time.

3. In a number of subjects, the observed electrocardiographic changes exceeded the normal limits previously established for the Master two-step test.

4. The pattern of cardiovascular response to exercise varied considerably from subject to subject. In general, the same subject showed similar patterns of response on repetition of the test.

5. A distribution grid for the simultaneous analysis of the response of pulse pressure and of heart rate is presented, which delineates nine different types of cardiovascular response to exercise.

6. The group of subjects showing the most marked increases both in pulse pressure and in heart rate after exercise were found to have an unusually high incidence of parental hypertension and/or coronary artery disease. Likewise, obesity, high resting blood pressure levels, transitory hypertension, high resting heart rate, transitory tachycardia and hyperreactivity to the cold pressor test were each more frequently encountered among the subjects with such circulatory hyperreactivity to exercise than among the total population of subjects.

7. The likelihood that individual constitutional differences are reflected in patterns of physiological responsiveness is discussed.

## APPENDIX

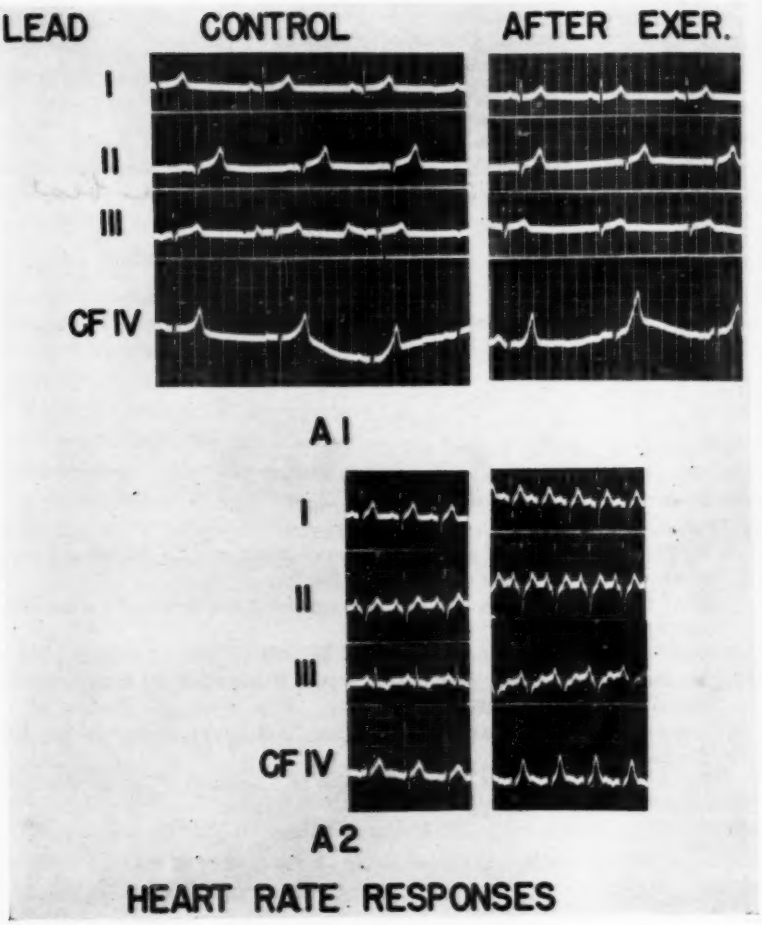
Examples of Electrocardiographic Changes after Exercise.

A. Types of Response of Heart Rate.
   1. Sinus bradycardia before and after exercise (51M27).
   2. Sinus tachycardia with gradual slowing (51M34).
   3. Sinus tachycardia alternating with sinus arrhythmia (48M56).
   4. Sinus tachycardia terminated abruptly by sinus arrhythmia (49M60).

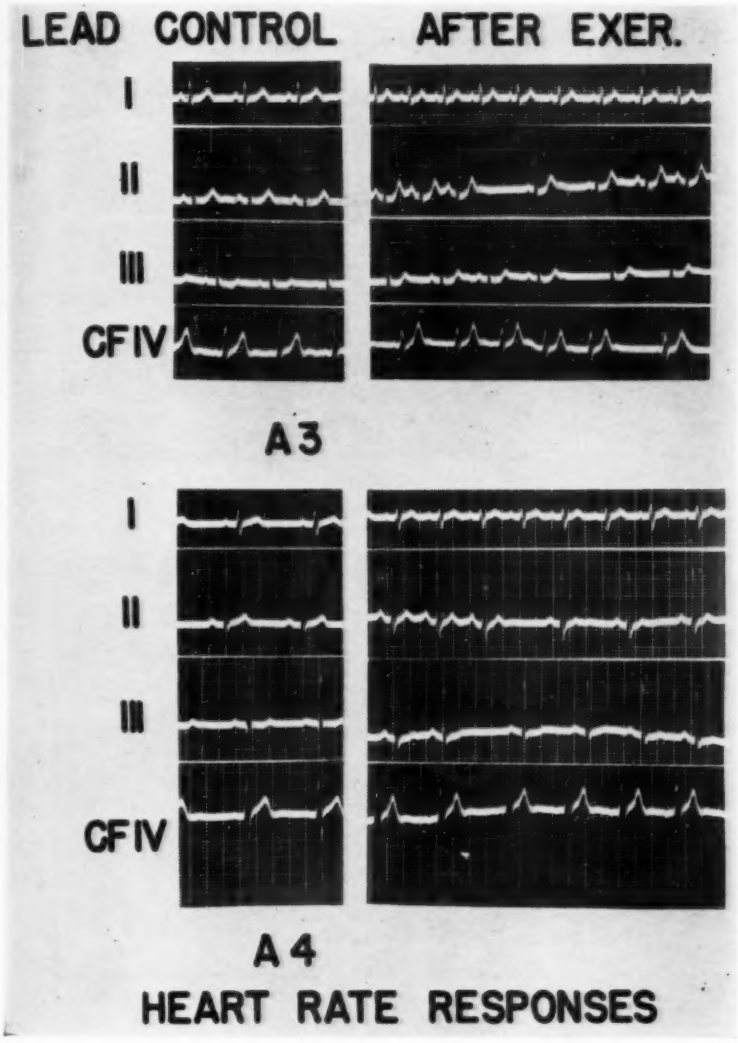
B. Types of Arrhythmias.
   1. Auricular premature beat in Lead CF IV (49M71)
   2. A-V nodal rhythm changed to normal sinus rhythm by exercise (52M40).
   3. Paroxysmal auricular tachycardia terminating early in Lead I (48M33).
   4. Paroxysmal auricular fibrillation in Lead CF IV preceded by interpolated premature beats in Lead III (52M12). (The ectopic rhythm is clearly visible despite the "ghost" shadow pattern resulting from imperfect alignment of the optical system of the electrocardiograph. See Sanborn Technical Bulletin, September, 1949.)

C. Types of T Wave Alterations.
   1. Diphasic T waves in Lead I (48W03).
   2. Diphasic T waves in Leads I and II (48M17).
   3. Diphasic T waves in Leads II and CF IV (49W37).
   4. Isoelectric T waves in Lead I (49M07).

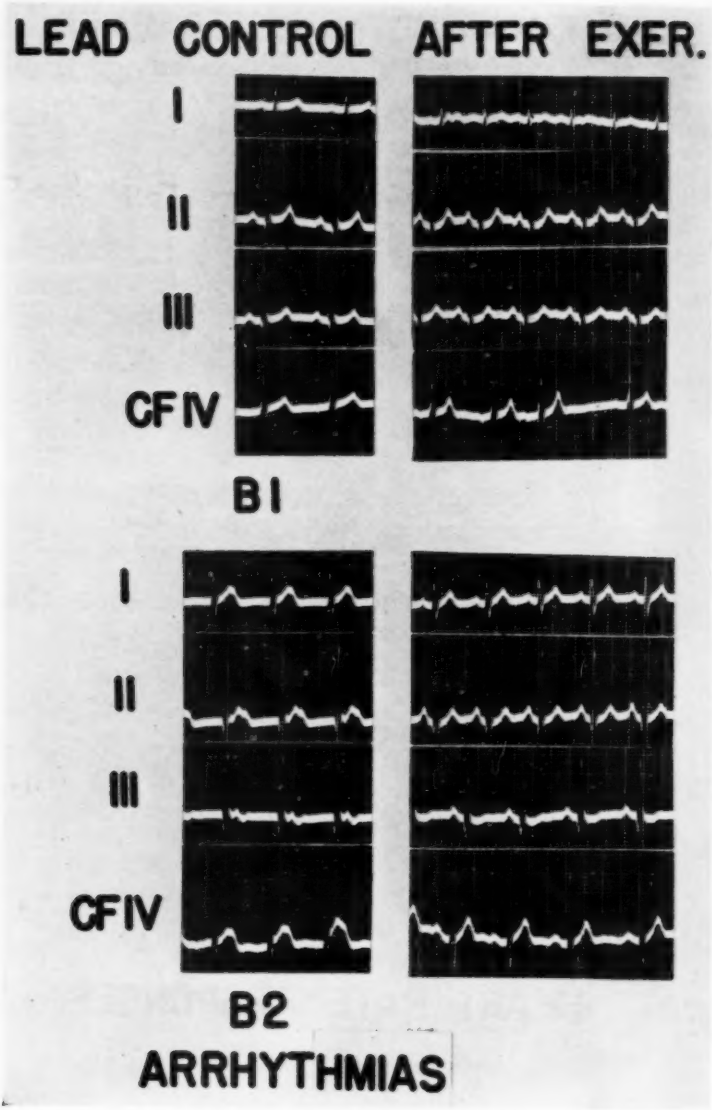
D. Types of RS-T Segment Changes.
   1. Well-marked elevation of RS-T segments in Leads II and CF IV before exercise, which was abolished after exercise (49M25).
   2. Sinus tachycardia after exercise without significant depression of the RS-T segments (48M36).
   3. Depression of RS-T segments in Lead III of more than 1.0 mm. (48M21). Standardization: 1 millivolt = a deflection of 10.2 mm. A 2% correction factor should therefore be subtracted.
   4. Depression of RS-T segments in Leads II and III of 1.0 mm. or more with diphasic T waves (48M19).
      Standardization: 1 millivolt = a deflection of 9.5 mm. A 5% correction factor should therefore be added.




HEART RATE RESPONSES




HEART RATE RESPONSES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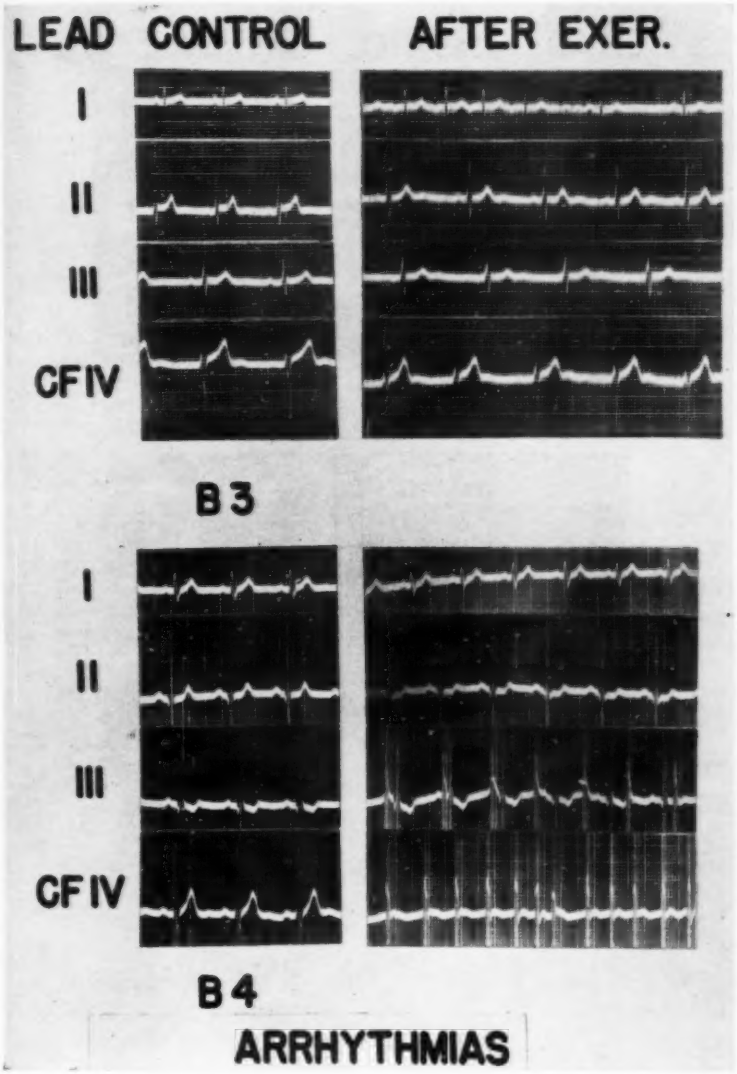
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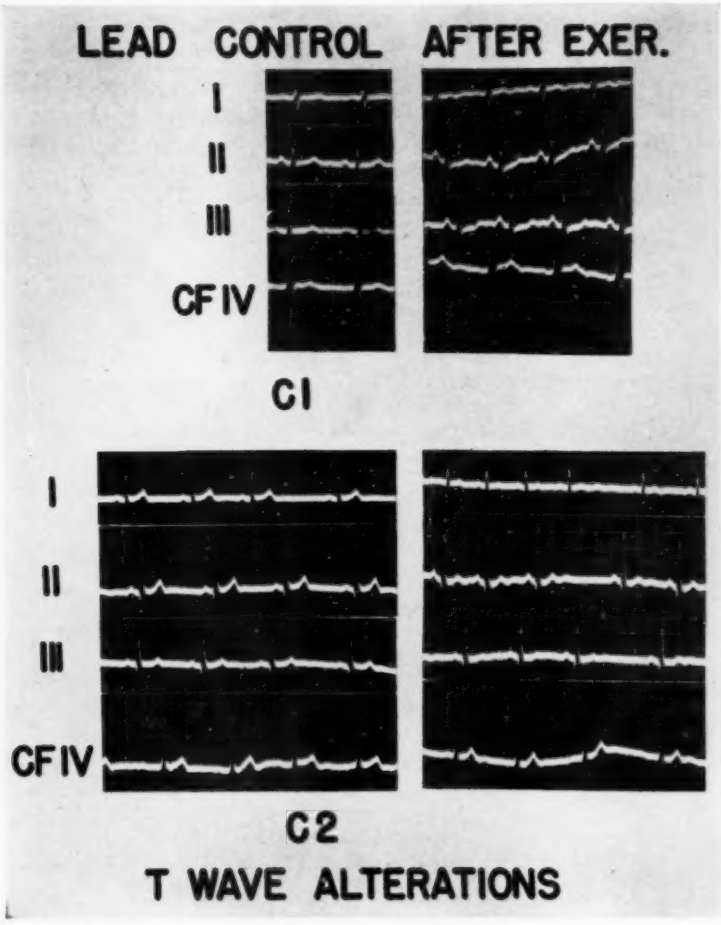
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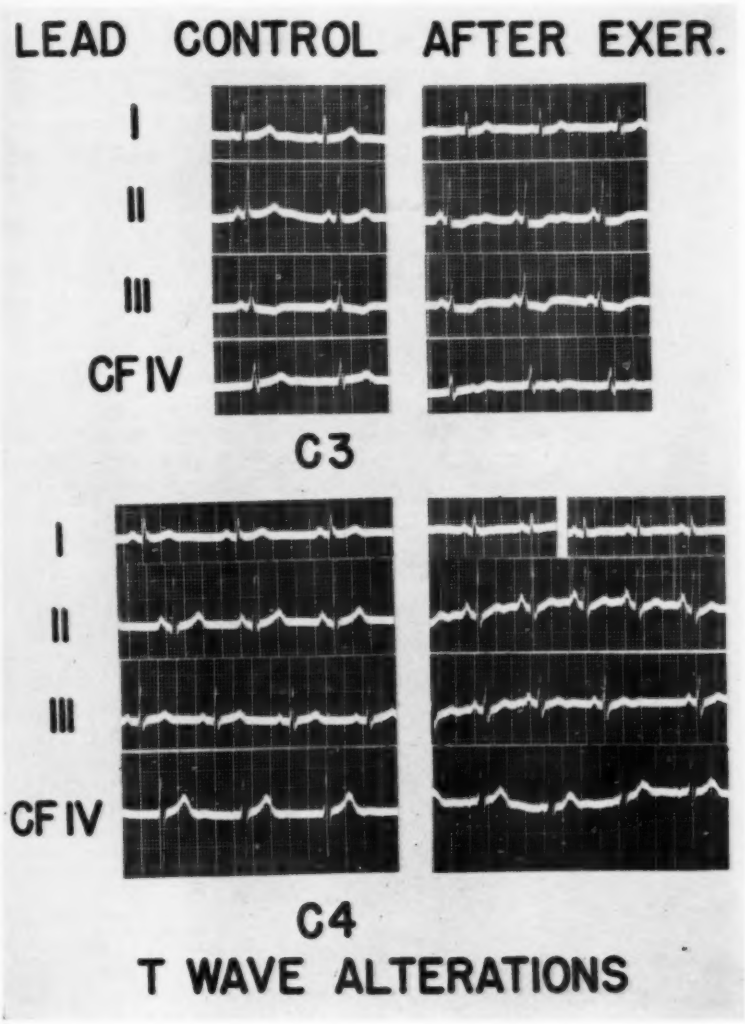
T WAVE ALTERATIONS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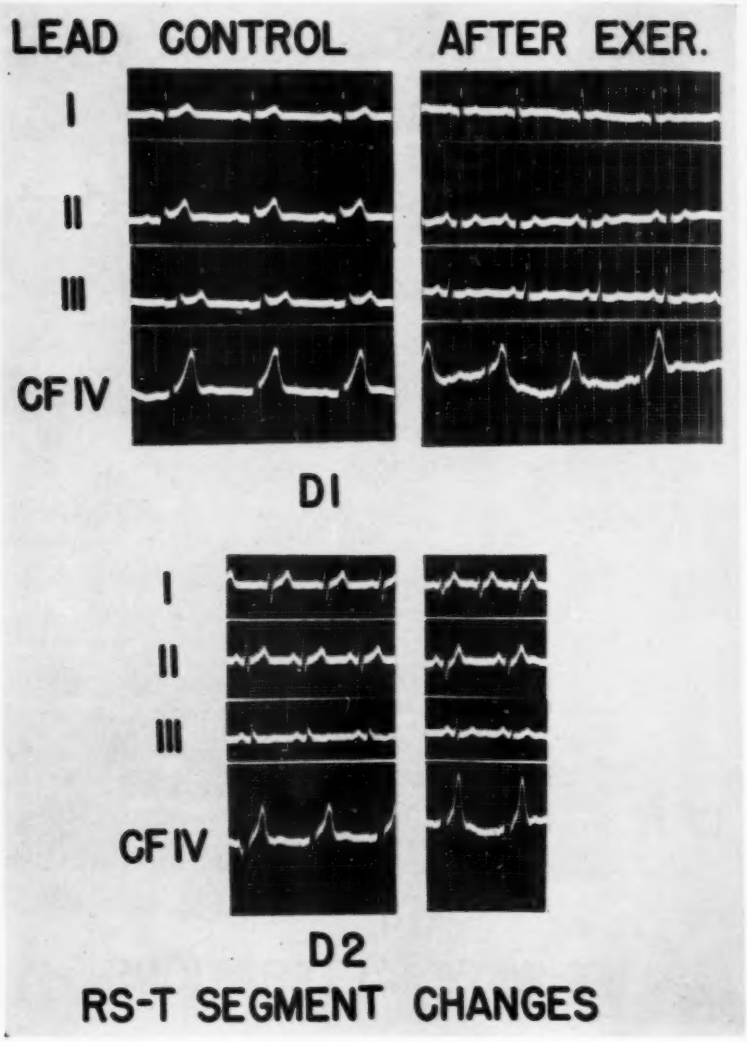
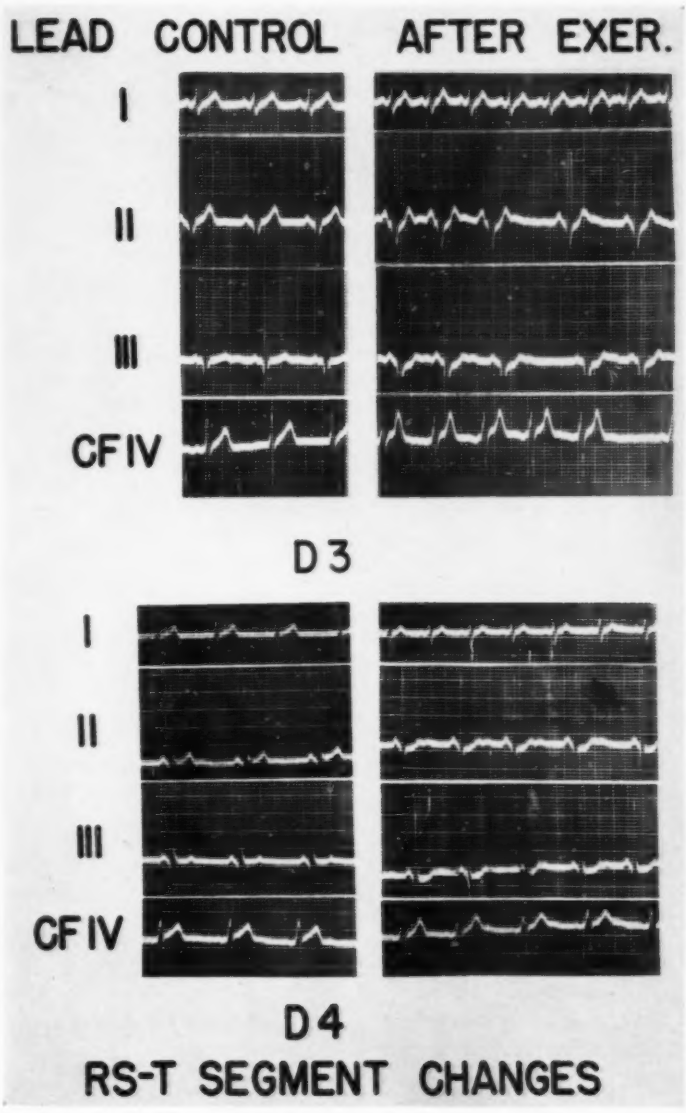



RS-T SEGMENT CHANGES


LEAD CONTROL AFTER EXER.
I
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D 4
RS-T SEGMENT CHANGES

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The following important reference was overlooked until after this paper was in press. Their electrocardiographic findings on subjects seventeen to fifty-seven years of age were in general similar to ours.

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# THE EFFECT OF CHOLINE DEFICIENCY ON THE DEVELOPMENT OF TUMORS PRODUCED BY BUTTER YELLOW*

JOHN J. BUCKLEY, SONJA M. BUCKLEY, AND ANNE E. SNIPES

*The Division of Laboratories and Research of the New York State Department of Health, Sloan-Kettering Institute for Cancer Research, and the Division of Experimental Chemotherapy, Sloan-Kettering Institute for Cancer Research, New York*

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Insidiously developing diffuse hepatic fibrosis, that is, diffuse nodular cirrhosis developing from a fatty infiltration rather than from necrosis of liver cells, was first demonstrated by Rich and Hamilton (1). These authors suggested that the condition was probbaly caused by choline deficiency.

That choline was the responsible agent was subsequently shown by Blumberg and McCollum (2) and others for a variety of animals. It has been reported that choline will rapidly reduce an increased fat content of the liver cells and that fatty infiltration can be produced by choline deficiency even though the diet contains very little fat (3).

Rich, Berthrong, and Germuth (4) have found that fat-laden hepatic cells caused by choline deficiency display a regenerative activity much lower than that of the non-fatty cells in the same liver. Thus the fatty liver seems to be at a distinct disadvantage when faced with demands for regeneration. From some of the evidence at hand, it would appear that the displacement of the cytoplasm of the hepatic cells by fat may interfere with mitosis mechanically, though it is possible that mitosis may be inhibited by a metabolic abnormality resulting from the choline deficiency.

In view of this lowered capacity for regeneration of hepatic cells that is produced by choline deficiency, it seemed of interest to investigate what effect, if any, choline deficiency would have on rats fed a diet containing butter yellow, a known liver carcinogen (5, 6). With this in mind, the following experiment was carried out.

## EXPERIMENTAL METHODS

Adult male Sherman rats, weighing 250–300 grams, were used. Four experimental groups, consisting of 50 rats each, were placed on the basal diet shown in table 1. This is the diet that was used by Rich, Berthrong, and Germuth (4) in their study of the regenerative capacity of fat-laden liver cells and, except for an increased amount of glycocyamine (7), is basically the diet used by Stetten and Grail (8) and Najjar and Ratcliffe (9) in their studies of the effect of glycocyamine. This diet is not choline free, but it has been shown that the addition of glycocyamine leads to the development of a fatty liver even when some choline is present in the diet (4, 8, 9), and that such fatty livers progress to diffuse nodular cirrhosis (4). There is evidence that, through its action as a strong methyl acceptor, glycocyamine depletes the

* This investigation has been supported through grants made to the Sloan-Kettering Institute for Cancer Research by the American Cancer Society.

supply of choline by combining irreversibly with methyl groups taken from the choline. The term "choline-deficient diet" will be used for convenience in referring to the glycocyamine-containing diet without additional choline supplement.

The basal diet was supplemented in group A with choline chloride (2 grams per 100 grams). In group B, choline chloride was omitted. In group C, butter yellow† was added in a concentration of 0.06 per cent, dissolved in cod liver oil. In group D, the basal diet was supplemented with choline chloride (2 grams per 100 grams) and butter yellow (0.06 gram per 100 grams).

TABLE 1

*Basal diet*

| | |
|---|---|
| Crisco | 35.0 grams |
| Casein | 15.0 " |
| Yeast | 6.0 " |
| McCollum's salt mixture | 4.0 " |
| $CaCO_3$ | 1.0 gram |
| Cod liver oil | 5.0 ml. |
| Sucrose | 32.0 grams |
| Agar | 2.0 " |
| Glycocyamine* | 2.0 " |

* Purchased from Daugherty Chemicals, 8734 134th Street, Richmond Hills, New York, and synthesized originally by Miss Mary Tompkins, Research Assistant in the Antibiotics Section of the Chemotherapy Division of this Institute, according to the method of Nencki and Sieber (7).

TABLE 2

*Average weight changes*

| GROUP | NUMBER OF RATS | WEIGHT AT BEGINNING | WEIGHT AT 5 MONTHS | AVERAGE WEIGHT CHANGE |
|---|---|---|---|---|
| | | *grams* | *grams* | *grams* |
| A | 45 | 255 | 329 | +74 |
| B | 47 | 260 | 311 | +51 |
| C | 46 | 270 | 259 | −11 |
| D | 48 | 288 | 306 | +18 |

Note: During the long feeding period, some of the animals succumbed to intercurrent infection.

The rats were supplied daily with an abundance of diet and water. The average weight change was recorded at monthly intervals. With the exception of eight rats of each group sacrificed especially for blood and bone marrow studies after a feeding period of five months, the remaining rats were sacrificed after approximately six months. Rats of all groups were autopsied in the same manner. An equal number of sections of liver, spleen, lung, heart, bronchial lymphnodes, thymus, pancreas, peripancreatic lymphnodes, both kidneys, and adrenals were taken and fixed in Zenker's solution for hematoxylin-eosin stains. Sections of liver were also fixed in formaldehyde for Sudan III stains.

## RESULTS

Clinically, the majority of rats in the four groups appeared to be in a good state of health. This was judged objectively by the average weight change ob-

† p-dimethyl-amino-azobenzene (No. 338, Eastman Kodak Company).

served during the experimental period. Table 2 shows the collective average weight change recorded after a feeding period of five months.

The histopathological findings were listed in accordance with Opie's observations (10) on the pathogenesis of liver tumors induced by butter yellow with the exception of the fatty infiltration of the liver as shown to be produced by choline deficiency.

TABLE 3

*Histopathological findings*

| TYPE OF LESIONS IN SURVIVING RATS | GROUPS | | | |
|---|---|---|---|---|
| | A | B | C | D |
| Number of rats at beginning | 50 | 50 | 50 | 50 |
| Number of rats after feeding period of 5 mos. | 45 | 47 | 46 | 48 |
| Nodular cirrhosis | 0 | 0 | 16 | 0 |
| Cystic ducts | 0 | 0 | 31 | 20 |
| Cholangiofibrosis | 0 | 0 | 17 | 11 |
| Hepatomas | 0 | 0 | 9 | 6 |
| Hepatomas with metastases | 0 | 0 | 0 | 16 |
| Cyst-adenomas | 0 | 0 | 0 | 0 |
| Cyst-adenomas with metastases | 0 | 0 | 0 | 0 |
| Cholangiomas | 0 | 0 | 4 | 4 |
| Cholangiomas with metastases | 0 | 0 | 0 | 0 |
| Fatty infiltration | 0 | all | all | 0 |
| Total number of rats with diffuse nodular cirrhosis | 0 | 0 | 16 | 0 |
| Total number of rats with tumors | 0 | 0 | 13 | 26 |
| Total number of rats with metastasizing tumors | 0 | 0 | 0 | 16 |

Table 3 summarizes the results obtained in the four groups in regard to liver lesions. The kidneys in groups B and C showed bilateral subcortical scarring, to a moderate degree, due to the choline-deficient diet. Studies on the blood and bone marrow will be described separately (11).

## DISCUSSION

In the present study three types of changes induced by butter yellow seemed to be of interest for the evaluation of choline deficiency in a diet containing butter yellow. They are (1) diffuse nodular cirrhosis, by which is meant diffuse scarring of the liver with, eventually, hyperplastic nodules of liver parenchyma surrounded by fibrous tissue (when well developed, this cirrhosis can be recognized macroscopically); (2) hepatic tumors of uncertain malignancy (hepatoma

or cholangioma), many of which can exhibit abundant mitoses; (3) definitely malignant tumors of hepatic origin. In accordance with Opie's interpretation, it has seemed desirable to identify decisively as malignant growths produced by butter yellow only those accompanied by metastases.

It would appear from the foregoing table that the toxic effect of butter yellow on the liver with resultant nodular cirrhosis, noted by various investigators and shown by Opie (12) to be dependent on the diet, can be greatly increased by a choline-deficient diet. This lesion is not present in group B (choline-deficient diet without butter yellow) or in group D (choline-deficient diet supplemented with butter yellow and choline chloride). As has been stated above, a choline-deficient diet, alone, will produce nodular cirrhosis. The basic diet used in the present study leads to choline deficiency, and this diet, itself, has been shown by Rich, Berthrong, and Germuth (4) to produce nodular cirrhosis. The addition of butter yellow in the present study enhanced the tendency of this diet to produce cirrhosis for, during the period of the experiment, cirrhosis developed only in the group receiving butter yellow.

Furthermore, butter yellow produced fewer tumors in the choline-deficient animals. Of greater importance, however, and quite striking was the apparent effect of choline deficiency on the metastasizing ability of butter yellow induced tumors. From our results, it is evident that on a high fat, low protein diet containing choline, 16 of 26 tumors that developed metastasized, whereas with the same diet in the absence of choline none out of thirteen tumor-bearing animals showed metastasis. While these tumors would probably have metastasized eventually had the experiment lasted for a longer period, the contrast between the incidence of metastases in groups C and D suggests, at least, that choline deficiency may exert an inhibitory effect on the reproductive capacity of cancerous hepatic cells. That tumors arise in choline-deficient animals may be explainable by the fact that in the fatty liver of choline deficiency there are often scattered small islands of liver cells which contain no fat and are quite capable of active division (4).

## SUMMARY

Feeding of butter yellow to rats rendered choline-deficient by the addition of glycocyamine to a low-choline diet results in the occurrence of nodular cirrhosis, a lesion not found in liver of rats similarly fed, but with choline supplement. Furthermore, the number of hepatic tumors produced by butter yellow in the choline-deficient animals during the period of the experiment was fewer than the number appearing in animals on the same diet with choline supplement. In addition, none of the tumors arising in the choline-deficient animals metastasized, whereas two thirds of the tumors arising in the animals with choline supplement metastasized.

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Plate I. Normal Rat Liver (Group A). (× 250)

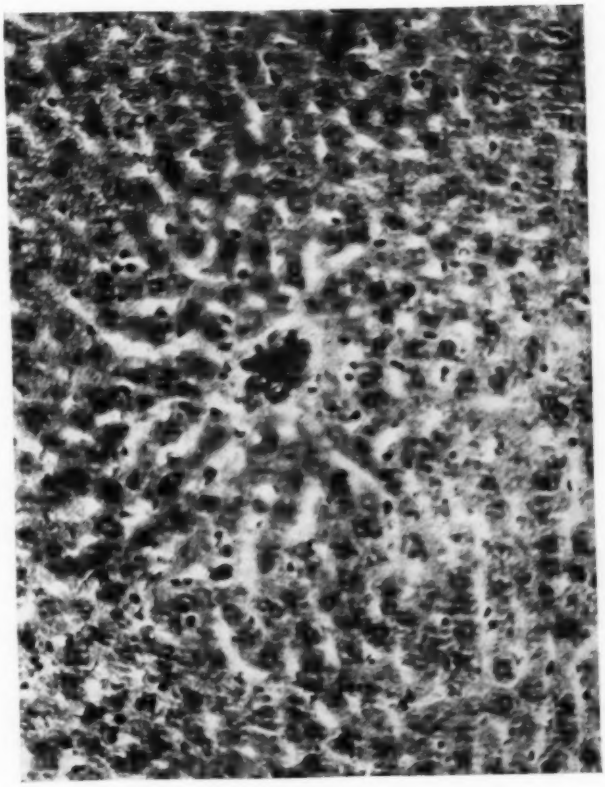

PLATE II. FATTY INFILTRATION OF LIVER (GROUP B). (× 250)

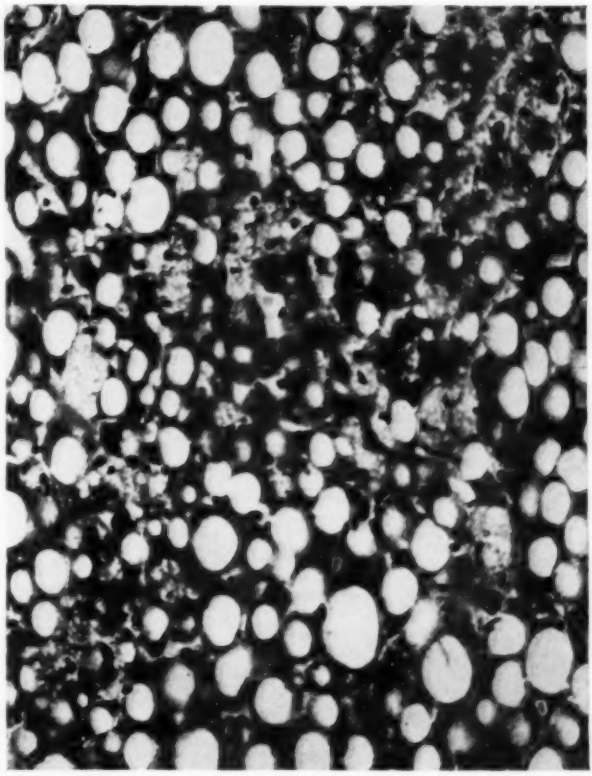

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PLATE III. DIFFUSE NODULAR CIRRHOSIS (GROUP C). (× 250)

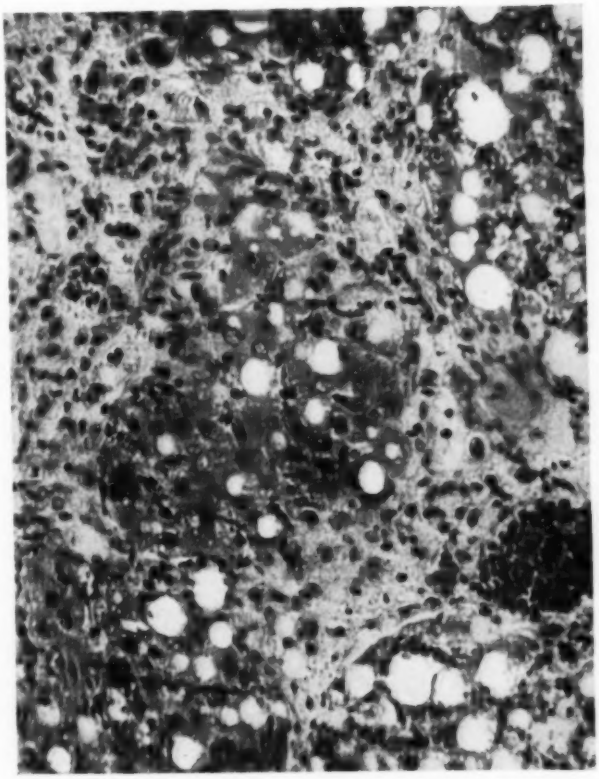

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PLATE IV. HEPATOMA (GROUP D). (× 250)

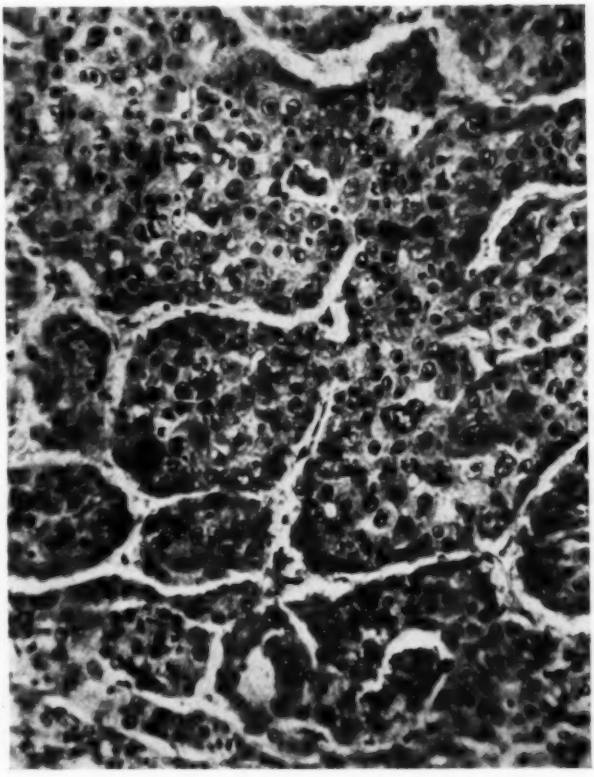

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PLATE V. METASTASIS OF HEPATOMA IN LUNG (GROUP D). (× 250)

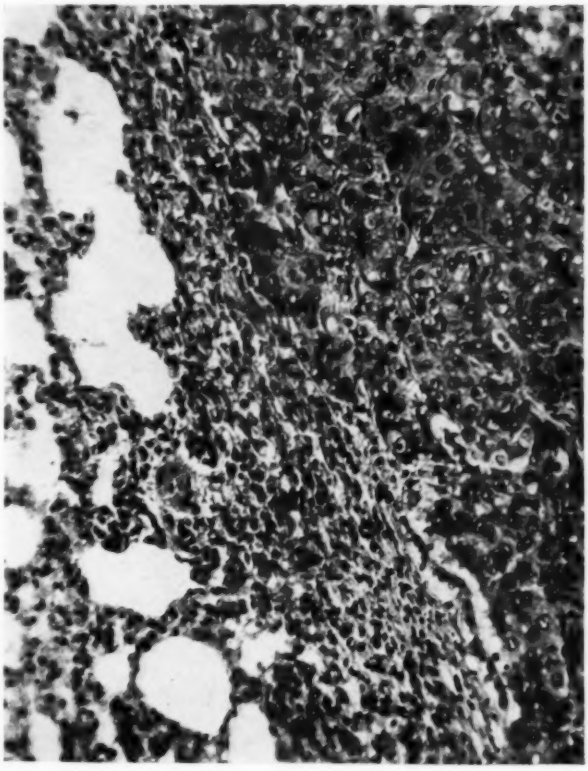

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PLATE VI. METASTASIS OF HEPATOMA IN BRONCHIAL LYMPHNODE (GROUP D). (× 250)

(× 250)

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# PHYSIOLOGICAL STUDIES IN CONGENITAL HEART DISEASE

## XII. The Circulatory Dynamics in Patients with Tricuspid Atresia*

BLOUNT, S. G., JR.,[1] FERENCZ, C.,[2] FRIEDLICH, A., MUDD, J. G.,[3] CARROLL, D. G.[4] AND BING, R. J.

*Department of Surgery, The Johns Hopkins University School of Medicine and Hospital*

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Previous papers of this series have dealt with methods and results obtained in physiological studies in patients with various congenital malformations of the heart. This report presents the physiological data obtained from the study of a group of patients with tricuspid atresia.

In this malformation the primary lesion is atresia of the tricuspid valve and as a result of this the right ventricle is poorly developed. Venous blood from the right auricle passes through a patent foramen ovale or an interauricular septal defect into the left auricle where it is mixed with blood returning from the lungs. Blood then passes through the mitral valve into the left ventricle and aorta. To reach the lungs, blood may pass either through a defect in the ventricular septum into the small, right ventricle and from there into the pulmonary artery or, if the ventricular septum is intact, through a patent ductus into the pulmonary artery. In some cases in which the ventricular septum is intact and the ductus has closed, blood may reach the lungs only through dilated bronchial arteries. The clinical findings in these cases are similar to those found in cases of tetralogy of Fallot (1). There is cyanosis and limitation of exercise tolerance. Squatting is not uncommon. A systolic murmur is usually present at the left sternal border and the pulmonary second sound is clear. The fluoroscopic appearance presents the characteristic picture of an underdeveloped right ventricle, concave pulmonary conus area and clear lung fields with minimal or absent pulsations in the hilar vessels. The electrocardiogram shows a left axis deviation and usually left ventricular hypertrophy.

### METHODS

The methods employed in these studies have previously been described in detail (2). For clarity's sake, the principal flow calculations are stated again:

The Fick principle has been applied to determine the volume of blood flow through various parts of the circulation.

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[1] Yedz Grotto, M.O.V.P.E.R. Fellow in Rheumatic Fever.

[2] U. S. Public Health Service Fellow of the National Heart Institute.

[3] Fellow in Medicine, Johns Hopkins University.

[4] William Steward Halsted Fellow in Surgery.



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1. Systemic blood flow is the volume of blood passing through the peripheral circulation per minute.

$$\text{Systemic Flow (ml./min.)} = \frac{O_2 \text{ consumed (ml./min.)} \times 100}{O_2 \text{ content of peripheral arterial blood (vol. \%)} - O_2 \text{ content of mixed venous blood (vol.\%)}}$$

2. Pulmonary artery blood flow is the volume of blood flowing through the pulmonic valve into the pulmonary vascular bed per minute.

$$\text{Pul. art. flow (ml./min.)} = \frac{O_2 \text{ consumed (ml./min.)} \times 100}{O_2 \text{ content of pul. vein blood (vol.\%)} - O_2 \text{ content of pul. art. blood (vol.\%)}}$$

3. The effective pulmonary blood flow is the volume of mixed venous blood which, after returning to the right atrium, eventually is aerated in the pulmonary capillaries.

$$\text{Eff. pul. flow (ml./min.)} = \frac{O_2 \text{ consumed (ml./min.)} \times 100}{O_2 \text{ content of pul. vein blood (vol.\%)} - O_2 \text{ content of mixed venous blood (vol.\%)}}$$

4. Intracardiac shunts are referred to as the volume of blood per unit time directed from one side of the heart to the other through septal defects. They are indicated as total right to left or total left to right.

The total right to left shunt is the volume of mixed venous blood that is shunted into the systemic circulation per minute. Total right to left shunt = systemic flow − effective pulmonary flow.

The total left to right shunt is the volume of fully oxygenated blood which is shunted into the pulmonary circulation per minute.

Total left to right shunt = pulmonary artery flow − effective pulmonary flow.

The differences between the right to left and the left to right shunt is referred to as the overall shunt. That is, the amount of blood which is actually added to either the systemic or the pulmonary circulation.

In the presence of an auricular defect, auricular blood does not represent truly mixed venous blood; therefore, the figure representing the oxygen content of mixed venous blood was obtained whenever possible, from the superior and inferior vena cava oxygen contents. In order to allow for the greater venous return via the inferior vena cava, a value was used which is closer to the inferior vena caval content by two thirds of the difference between the caval oxygen contents.

## RESULTS

Three patients were studied by the method of cardiac catheterization in whom the diagnosis was corraborated by the necropsy findings. Clinical findings in two of these patients (H. G. and A. A. M.) are presented in detail. The physical findings on the third (P. E.) are included in the chart.

Seven other patients have been studied by cardiac catheterization in whom the probable diagnosis was tricuspid atresia. As portmortem findings are not available, the data obtained from study of these patients are presented in chart form only (Table I).

TABLE I

*The Findings Obtained by Catheterisation in Ten Patients with Tricuspid Atresia*

| CASE NO. | NAME | AGE | SEX | SURFACE AREA | BLOOD OXYGEN CONTENT, VOLUMES % | | | | | | | | INDICES | | SHUNT | PRESSURE mm Hg | | | | METABOLISM | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SVC | IVC | RA | LA | LV | FA | PV | Cap | % Sat | Systemic | Effective | Total R→L | RA | LA | LV | FA | $O_2$ cons. cc./min. | M.V. Lit. | E.K.G. | Surgery |
| 1. | H. G. | 26 | F | 1.68 | 15.6 | | 14.6 | | 18.4 | 18.5 | 31.9 | 33.6 | 55 | 3.7 | .835 | 2.865 | 30/17 | | 142/17 | 130/86 | 242 | 5.83 | Lad. | yes |
| 2. | A. M. | 4 | F | 0.5 | 9.56 | 9.14 | 9.93 | 12.18 | 13.62 | 11.90 | 24.82† | 25.88 | 46 | 6.4 | 1.10 | 5.3 | 34/24 | | 86/37 | | 85‡ | | Lad. | yes |
| 3. | A. B. | 6 | F | 0.8 | 16.40 | 14.52 | 16.52 | 20.4 | 20.6 | 19.26 | 27.2† | 28.0 | 68.9 | 4.30 | 1.31 | 2.99 | 20/15 | 18/11 | 130/0 | | 119 | 4.76 | Lad. | no |
| 4. | J. C. | 12 | F | 1.0 | 14.12 | | 14.61 | 17.98 | 19.5 | 19.5 | 23.6† | 24.4 | 80 | 1.68 | 1.0 | .68 | 18/12 | 24/7 | 138/0 | | 90.5 | 5.32 | Lad. | no |
| 5. | S. K. | 21 | M | 1.64 | 19.91 | 17.03 | 18.93 | 22.35 | 23.00 | 24.4 | 26.13 | 29.8 | 82 | 2.3 | 1.4 | .9 | 12/10 | 12/6 | 86/12 | | 239 | | Lad. | yes |
| 6. | W. M. | 9 | M | 1.01 | 21.9 | | 20.7 | | 26.1 | 25.1 | 36.0† | 37.9 | 66.2 | 4.25 | 1.22 | 3.03 | | | | | 185 | 7.64 | Lad. | yes |
| 7. | R. S. | 21 | M | 1.54 | 16.1 | 19.3 | 17.9 | | | 23.3 | 28.6† | 30.1 | 77 | 2.26 | 1.16 | 1.1 | | | | | 196 | 10.64 | Lad. | yes |
| 8. | P. W. | 11 | F | 0.87 | 14.7 | | 16.6 | | | 21.5 | 25.5† | 26.7 | 80.3 | 2.12 | 1.33 | .79 | 32/17 | | | 115/73 | 125‡ | | Lad. | no |
| 9. | P. C. | 6 | F | 0.80 | 15.18 | 15.65 | 15.40 | 25.45 | | 18.65 | 25.40 | 27.33 | 68.2 | 4.3 | 1.40 | 2.90 | 13/6 | | | | 112 | | Lad. | yes |
| 10. | P. E.* | 7 | F | .73 | 17.74 | 17.81 | 20.95 | 26.41 | | | 28.59 | 29.5 | | | | | | | | | 97 | | Lad. | no |

* Diagnosis proven by autopsy.
† Calculated.
‡ Assumed.

*Case 1.* H. G. (Date of study, February 26, 1947). This 26 year old white female was admitted because of cyanosis and dyspnea which had been present since birth. She had not been greatly handicapped until the year preceding the examination, but since that time she had progressively become worse. At the time of examination she was able to walk but one block. She squatted frequently to rest. Slight exertion invoked severe dyspnea and intensification of her cyanosis. There was no history of paroxysmal dyspnea, convulsions or hemoptysis. There had been questionable dependent ankle edema for the two weeks prior to admission.

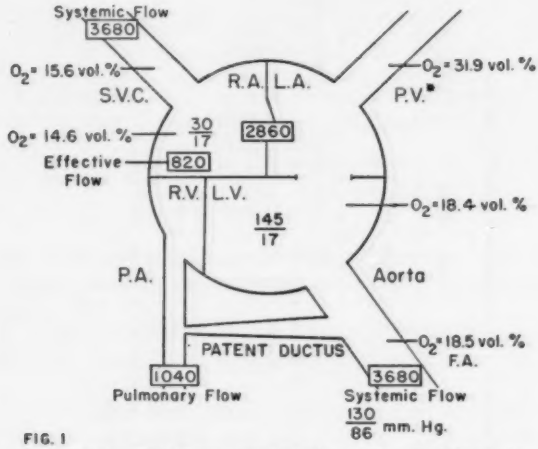


FIG. 1
Circulatory Diagram Illustrating the Findings in Case I (H.G.).

FIG. 1. There was a significant rise in oxygen content from right auricle to the ventricle which was catheterized via the foramen ovale and the left auricle. The oxygen contents of blood in the ventricle and in the femoral artery were identical, demonstrating a functional single ventricle. Blood reached the pulmonary artery through a patent ductus. The effective pulmonary flow was low.

Physical examination revealed a well developed, cyanotic young woman who was slightly orthopneic. There was marked suffusion of her conjunctivae and deep cyanosis of her mucous membranes. The pulse rate was 92 with normal sinus rhythm. The blood pressure was 120/90 in both arms. The lungs were clear to percussion and auscultation. There was no deformity of the precordium. The pulmonic second sound was pure. There was a faint systolic murmur over the pulmonic area. The abdomen was soft and the liver edge was palpable 3 centimeters below the right costal margin. No pulsations were felt. The spleen was just palpable below the left costal margin. There was marked clubbing of the extremities. Peripheral pulses were all present and slight pitting edema of the ankles was noted. The remainder of the physical examination disclosed nothing of significance.

The electrocardiogram showed definite left axis deviation, but the pattern in the chest leads suggested right ventricular hypertrophy.

Fluoroscopy of the heart revealed considerable cardiac enlargment. In the AP view there was a prominent and vigorously pulsating aortic knob and a marked concavity in the region

of the pulmonary artery. The hilar shadows were small and revealed a large number of fine radiating markings spreading out into the lung field; none were expansile.

In the L.A.O. projection a moderate degree of enlargement of both ventricles was visualized and the aorta appeared large. The pulmonary window was hazy. The esophagram indicated a left aortic arch.

Laboratory studies revealed a hematocrit of 85.7 per cent, a hemoglobin of 24 grams and a red blood count of 10.4 million.

Angiocardiography was performed by Dr. Robert Cooley of the Department of Radiology. It was his opinion that the findings were compatible with a "triloculate heart."

### *Physiological Studies*

Pertinent data obtained from cardiac catheterization are shown in Figure 1. The significant findings included:

1. The left ventricle was entered via the left atrium after passing through an auricular defect.
2. The oxygen content of blood from this high pressure chamber was 3.8 vols.% higher than that of blood from the right atrium.
3. The oxygen content of peripheral arterial blood was essentially the same as that of the ventricle.
4. The oxygen saturation of peripheral arterial blood was 55 per cent.
5. The pressure within the ventricle was 145/17 mm. Hg and that within the femoral artery was 130/86 mm. Hg. The right atrial pressure was 30/17 mm. Hg.
6. The systemic blood flow was 3680 cc/min/$M^2$ while the effective pulmonary blood flow was only 820 cc./min/$M^2$.
7. The right to left shunt amounted to 2860 cc/min/$M^2$.
8. Neither the pulmonary artery nor the aorta was catheterized.

### *Comment*

The increase in oxygen content of 4 vol.% from the right atrium to the ventricle was suggestive of the presence of a functional single ventricle (3). The finding that the oxygen content of the peripheral arterial blood was identical with that of the ventricle lends further support to this contention.

The systemic flow was slightly above normal while the effective pulmonary flow was low.

The total right to left shunt was of considerable magnitude as would be expected from the degree of peripheral arterial unsaturation.

The pressure within the ventricle was similar to that determined by direct puncture of the femoral artery.

With the purpose of creating an artificial ductus a right thoracotomy was performed by Dr. Alfred Blalock. During the operation the heart action suddenly ceased and despite all therapeutic measures the patient expired.

Postmortem examination was performed by Dr. Thomas Payne of the Department of Pathology. Significant findings were as follows:

The heart weighed 500 grams. The great veins entered the right atrium and the only exit for this blood was through a widely patent foramen ovale. The tricuspid valve was atretic. The mitral valve was normal and communicated with the greatly hypertrophied left ventricle. The aorta arose from it in a normal position. The right ventricle was a rudimentary and non-functioning chamber. The pulmonic valve was normal. There was a ductus arteriosus, widely patent on the aortic side, measuring about 1 cm. in the greatest diameter. It was funnel-shaped with the larger end on the aortic side while on the pulmonic side the orifice

was almost completely occluded by a small vegetative-like mass of thrombus, which apparently cut off almost all of the pulmonary circulation. However, a probe could still be passed through the pulmonary end of the ductus. No dilated bronchial arteries were visible and the ductus would seem to have been the only source of pulmonary blood. The pulmonary artery was very short, but its diameter was within normal limits.

*Case 2.* A. A. M. (Date of study, July 8, 1949). This 4 year old girl was said to be normal at birth. On the third day of life cyanosis appeared and gradually increased in severity. She had been dyspneic since infancy and experienced frequent and severe attacks of paroxysmal

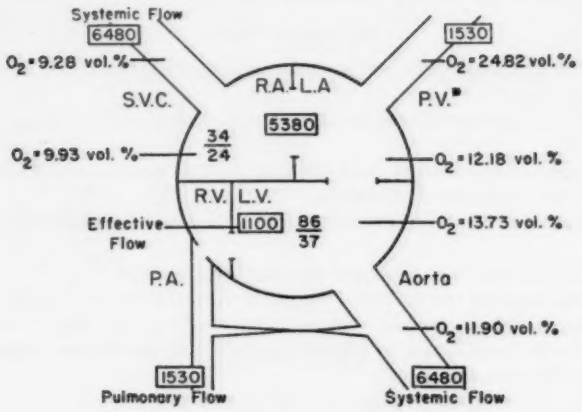


FIG. 2
Circulatory Diagram Illustrating the Findings in Case 2 (A.A.M.)

FIG. 2. In this patient the catheter entered the left ventricle where the blood oxygen content was higher than the aortic blood oxygen content, probably due to streamlining. The ductus was closed. Blood entered the pulmonary artery via the small right ventricle and ventricular septal defect.

dyspnea, with loss of consciousness on many occasions. Her exercise tolerance had been limited to walking one block but more recently she had not been able to walk at all. A few weeks prior to hospitalization edema of the face and legs and swelling of the abdomen were noted.

On physical exmination the child appeared poorly developed and poorly nourished. The eyes showed some suffusion and the mucous membranes were markedly blue. Cyanosis was uniform and marked. There was clubbing of fingers and toes. There was a bulge of the left precordium. The heart rate was 120 with regular sinus rhythm, and the character of the pulse was good. The blood pressure in the arms was 110/90 mm. Hg and that in the legs was 130/110 mm. Hg. The apex beat was seen and palpated in the 6th interspace in the anterior axillary line. There was a loud, harsh systolic murmur along the left sternal border maximal in the 3rd and 4th interspace. The second pulmonic sound was sharp and clear.

The lungs were clear to ausculation and percussion.

The abdomen was protuberant and the liver was palpable four fingersbreadth below the right costal margin. It was firm, slightly tender and no pulsations could be felt. The spleen was not felt. There was slight pitting edema of the ankles.

The electrocardiogram revealed left axis deviation and the configuration of the ST segments and QRS complexes suggested left ventricular hypertrophy and strain.

Fluoroscopy revealed the heart to be greatly enlarged, especially the left ventricle and the right atrium. The base of the heart was narrow, both in the antero-posterior and the oblique views. The lung fields appeared clear.

Laboratory studies revealed a hematocrit of 73 per cent, a hemoglobin of 20.5 grams and red blood cell count of 9.15 millions.

### *Physiological studies*

Pertinent data obtained from cardiac catheterization are shown in Figure 2. Significant findings include:

1. The oxygen content of the blood sample from the right auricle was 9.93 vol.%, an increase of but .65 vol.% above the mixed venous sample calculated from the oxygen content of vena caval blood, (9.28 vol.%). A blood sample obtained from the left atrium revealed an oxygen content of 12.18 vol.%, an increase of 2.90 vol.% over the calculated oxygen content of mixed venous blood.
2. The oxygen content of the ventricular blood sample was 3.80 vol.% higher than that of the right atrial blood. Femoral artery oxygen content was 1.83 vol.% lower than the oxygen content of the ventricular blood.
3. The oxygen saturation of peripheral arterial blood was 46 per cent.
4. The left ventricle was entered from the left atrium via the atrial septal defect.
5. The systemic blood flow was 6480 cc./min./$M^2$, the effective pulmonary blood flow was 1100 cc./min/$M^2$. The right to left shunt was 5380 cc./min/$M^2$.
6. Neither the pulmonary artery nor the aorta was catheterized.
7. The pressure within the ventricle was 86/37 mm. Hg and the pressure within the right auricle was 34/24 mm. Hg.

### COMMENT

There was no conclusive evidence of left to right shunt in the atria since the oxygen content of the blood sample from the right atrium was but 0.65 vol.% higher than the oxygen content of calculated mixed venous blood. This bears out the observation described in a previous publication (4) that in cases of tricuspid atresia the pressure gradient is usually from right atrium to the left during the whole of the cardiac cycle.

The oxygen content of a blood sample obtained from a low pressure area was 12.18 vols.%. This was 2.90 vols.% higher than the calculated mixed venous blood. This observation together with the fluoroscopic position of the catheter, indicated that the left atrium had been entered. The rise in blood oxygen content of 3.69 vols.% from the right atrium to the ventricle was suggestive of the presence of a functional single ventricle. The systemic blood flow was high while the effective pulmonary blood flow was very low. The large right to left shunt is reflected in the low peripheral arterial saturation of 46 per cent.

On the 26th of July, 1949, a right thoracotomy was performed by Dr. Alfred Blalock under cyclopropane-ether anesthesia. The heart action was very poor from the start, and the heart stopped on several occasions during the operation but responded to epinephrine and massage.

An end to end anastomosis between the right subclavian and the right pulmonary artery was accomplished. A fair thrill could be felt in the pulmonary artery following the procedure. However, the patient died an hour after operation.

Postmortem examination was performed by Dr. David Sabiston of the Department of Pathology. Significant findings were as follows:

The heart was large, weighing 160 grams and was dilated. The venous return was normal.

There was essentially a single atrium; the atrial septum consisting only of a few delicate strands of web-like fibrous tissue. There was atresia of the tricuspid valve and a very small right ventricle with a chamber of less than 10 cc. capacity from which the pulmonary artery arose. The pulmonary valve was bicuspid and had a circumference of 3 cm. The pulmonary arteries appeared normal. The mitral valve was normal, opening into the hypertrophied left ventricle. Beneath the anterior aortic cusp there was a small defect in the ventricular septum of 3–4 mm. in diameter, opening into the right ventricle about 2 cm. below the pulmonic valve ring. The aorta arose normally. An obliterated ductus was present. The bronchial arterial orifices were not definitely enlarged, and no large pulmonary collaterals could be identified.

## DISCUSSION

In patients with tricuspid atresia the only possible exit for blood from the right atrium is through a patent foramen ovale or an atrial septal defect. In the left atrium there is mixing of caval blood with blood returning from the pulmonary veins. The blood then enters the left ventricle through the mitral valve and reaches the lung by one of two courses, either via a ventricular septal defect through to the diminutive right ventricle into the pulmonary artery or through a patent ductus or collateral vessels from the aorta. A ventricular septal defect is present in most patients with tricuspid atresia. In Maude Abbott's analysis of 1000 cases of congenital heart disease there are sixteen cases of tricuspid atresia, fourteen of which had a ventricular septal defect (5). In some cases transposition of the great vessels may be present in addition to the tricuspid atresia. Tricuspid atresia must be distinguished anatomically from a single ventricle with a rudimentary outlet chamber. In tricuspid atresia the mitral valve leads to the left or common ventricle, whereas in an anatomical single ventricle, both tricuspid and mitral valves enter a common ventricle and the rudimentary outlet chamber represents persistence of a portion of the bulbus cordis and is separated from the common ventricle by a muscular ridge. The differentiation between anatomical single ventricle and tricuspid atresia by catheterization alone is sometimes difficult. In both malformations the catheter enters a high pressure area in which the blood has a relatively high oxygen content. In the patients of this series, the difference in oxygen content between right auricular and ventricular blood exceeds 3.5 volumes per cent, indicating the presence of a functional single ventricle. However, tricuspid atresia may be recognized if on withdrawing the catheter from the high pressure area into the right auricle it first passes through a low pressure area containing blood of a similarly high oxygen content.

There is another finding which suggests the presence of tricuspid atresia. This is the inability to pass the catheter into a high pressure area. It may be noted from Table I that in four of the ten patients a high pressure area was not entered. Similar difficulties are only encountered in the presence of a greatly dilated right atrium.

A further finding of interest is that neither the aorta nor the pulmonary artery were intubated in any of the ten patients. The systemic blood flow ranged from 1.68 to 6.48 l./M²/min. in the patients of this series. A similar wide range was found in patients with the tetralogy of Fallot. Although the patients were not studied under basal conditions, it is possible that the wide range was the result of variations in peripheral systemic resistance (6). The pulmonary artery blood flow cannot be calculated as the pulmonary artery was not intubated in any of the patients. Hence the magnitude of the left to right shunt cannot be determined. If it is assumed that the pulmonary arterial oxygen content is the same as that of the ventricle, a theoretical pulmonic flow can be calculated. This was found to be markedly reduced in all of these patients. The effective pulmonary flow was greatly reduced in the two patients with proven tricuspid atresia being .820 L/min./M² in case No. 1 and 1.10 L/min./M² in case No. 2. Similar low effective pulmonary flows were found in the other patients of this series.

In patients in whom a patent ductus arteriosus is also present the effective pulmonary blood flow might be adequate to meet the oxidative requirements of the body. This would depend upon the calibre of the patent ductus arteriosus and the relative resistances of the pulmonary and systemic vascular beds. Even if the pulmonary artery had been intubated, the diagnosis of a patent ductus arteriosus could not have been made by catheterization. In patients with a functional single ventricle, the oxygen content of the blood from the aorta is probably the same as the oxygen content of blood in the pulmonary artery.

It is apparent that in patients with tricuspid atresia the pulmonary artery flow and the effective pulmonary flows were reduced. Since a right to left shunt is also present, the patient can be benefited by a shunting operation (7).

## SUMMARY

Ten patients with tricuspid atresia were studied by cardiac catheterization. In this malformation, venous blood reaches the lung either through a ventricular defect, a patent ductus or collateral bronchial vessels.

The difference in oxygen content between right auricular and ventricular blood exceeded 3.5 vol. per cent, indicating the presence of a functional single ventricle. For this reason differential diagnosis between anatomical single ventricle and tricuspid atresia is difficult by means of catheterization. However, in tricuspid atresia a low pressure area with high oxygen content was encountered on withdrawing from the high pressure area into the right auricle. Furthermore, neither the aorta nor the pulmonary artery were entered.

As in the tetralogy of Fallot, large variations in systemic blood flow were encountered in patients with tricuspid atresia. There was a reduction in pulmo-

nary artery and effective pulmonary blood flow. A reduction in the pulmonary artery flow as compared to the systemic flow is of diagnostic significance because a relatively low pulmonary flow excludes the possibility of a single ventricle with transposition of the great vessels.

The physiological findings indicate that a shunting operation is of benefit in tricuspid atresia.

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# THE RÔLE OF SURFACE AND OF CALCIUM IN THE COAGULATION OF A GLOBULIN FRACTION OF PLATELET-DEFICIENT PLASMA

OSCAR D. RATNOFF AND C. LOCKARD CONLEY

*The Department of Medicine, The Western Reserve University and the Mt. Sinai Hospital, Cleveland, and the Department of Medicine, The Johns Hopkins University and Hospital*

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There is good evidence that the conversion of prothrombin to thrombin in shed blood may be initiated in some manner by a soluble substance or substances present in plasma. This substance, sometimes called plasma thromboplastic factor, is thought to be present in the circulating blood in the form of a precursor. It has been suggested that this precursor may be activated upon contact with glass surfaces (1, 2). This hypothesis is based on the observation that essentially platelet-free plasma, obtained without the use of anticoagulants, either failed to clot or clotted only after a long interval when incubated in tubes coated with silicone. Such plasma, however, clotted within a relatively short time when it was placed in glass tubes (2).

In the course of studies of the proteolytic activity of plasma, it was noticed repeatedly that the euglobulin fraction containing the greatest enzymic activity often clotted spontaneously. Further evidence that a factor in plasma is activated by glass surfaces has been obtained by a study of the clotting properties of this globulin fraction. The globulin was prepared from plasma from which the platelets had been removed, and in such a way that contact with glass surfaces was avoided. Under these conditions, the euglobulin did not clot. However, when the fraction was transferred to tubes containing crushed glass, coagulation took place. On the other hand, the globulin prepared from hemophilic plasma either failed to clot in glass tubes, or clotted only after a prolonged interval. Since hemophilic plasma contains normal amounts of prothrombin, accelerator globulin and fibrinogen, it is probable that the glass did not act on any of these substances. For this reason it was concluded that crushed glass probably activated a substance which was evidently deficient in hemophilic plasma. In turn, this substance initiated the conversion of prothrombin to thrombin.

The calcium content of the globulin fraction under study was relatively low. When the concentration of calcium ions was increased to that normally present in whole blood, clotting of the normal globulin occurred promptly in silicone treated tubes. Under these conditions, the conversion of prothrombin to thrombin occurred in the absence of platelets or glass surfaces.

## METHODS

*Nomenclature:* The term *globulin* is used to refer to a crude fraction precipitated from diluted plasma by acidification to approximately pH 5.3. In no sense does the term imply a purified protein. This fraction is known to contain such substances as prothrombin, fibrinogen, accelerator globulin, plasma thromboplastic factor, mid-piece of complement, and the precursor of the proteolytic enzyme of plasma, as well as an unidentified accelerator of clotting described in an earlier report. (3) The term *plasma thromboplastic factor* designates the substance or substances in plasma which, under certain conditions, may initiate the conversion of prothrombin to thrombin. This factor appears to be related to the antihemophilic substance in plasma. Presumably, it is present in plasma in the form of an inactive precursor. *Native plasma* refers to plasma obtained without the addition of an anticoagulant and freed from formed elements by centrifugation.

*Preparation of Globulin:* Blood was drawn without the addition of an anticoagulant, using silicone-treated equipment. Platelet-deficient plasma was prepared by techniques previously described. (2, 4) The formed elements including the platelets were removed by centrifugation for 10 minutes at 10,500 rpm in a Servall SS-1 angle centrifuge in the cold. (4) Plasma prepared in this way uniformly contained less than 50 platelets per $mm^3$. The plasma was kept until used in a silicone-lined lusteroid tube placed in a beaker containing ice and water. This plasma, then, was not permited to come in contact with glass surfaces and was essentially platelet-free.

The globulin fraction was precipitated by diluting one volume of plasma with 19 volumes of distilled water, and acidifying the diluted plasma with one per cent acetic acid to pH 5.2 to 5.4. The pipettes and glassware used were coated with silicone, and the pH was determined with color indicators to avoid any contact of plasma with glass. The precipitated globulin was separated by centrifugation at 2500 rpm in a Servall Model G-1 angle centrifuge at room temperature. The supernatant fluid was decanted and the precipitate was dissolved in buffer in a volume equal to that of the original sample of plasma. The *buffer* solution consisted of 7.30 grams of sodium chloride, 2.76 grams of barbital, and 2.06 grams of sodium barbital, diluted to a volume of one liter with distilled water. The buffer was thus composed of 0.125M sodium chloride, buffered by 0.025M barbital at pH 7.5.

*Preparation of Crushed Glass:* Pyrex glass was crushed until the particles passed through a 60 mesh screen but were retained by a 100 mesh screen. This crushed glass was used repeatedly without apparent loss of activity, and was cleaned with chromic acid, rinsed with distilled water, and dried before each use.

*Preparation of Thromboplastin:* Five hundred mg. of commercial thromboplastin (Chilcott), prepared from rabbit lung, were crushed in a porcelain mortar and mixed with 20 ml. of 0.85 per cent solution of sodium chloride. The mixture was heated at 50° C. for 10 minutes, and the grossly particulate material was removed by centrifugation at 2,500 rpm for 15 minutes. For seven days, the supernatant suspension was dialyzed in Visking No-Jax cellophane sausage casings at 4° C. against frequent changes of buffer. At the end of this period, the thromboplastin was still active. It was stored in an electric refrigerator at −10° C.

*Measurement of Clotting Time:* Clotting times were determined in Pyrex Wassermann tubes with an internal diameter of 11 mm. Some of these tubes were lined with silicone Others contained measured amounts of crushed glass. The tubes were submerged in an ice bath and suitable amounts of the solutions to be tested were added in succession to each tube. After thorough mixing, the tubes were transferred to a water bath at 37° C., and the clotting times were determined in duplicate. The second tube was not disturbed until the

first had clotted. Sometimes clotting did not seem to be complete. Such clots were recorded as partial clots. The tubes were observed for a period of 24 hours. During this period, the clots usually lysed completely. After 24 hours, 0.2 ml. of a solution of thrombin[1] containing 20 National Institutes of Health units per ml. was added to each tube. The formation of a clot after the addition of thrombin was evidence that complete clotting had not taken place during the preceding 24 hours. The converse was not necessarily true. The absence of clotting after the addition of thrombin could be interpreted to mean that clotting had occurred, followed by fibrinolysis. However, the absence of clotting could also be interpreted as signifying that the fibrinogen present had been digested by the proteolytic enzyme of plasma.

*Determination of Calcium:* The concentration of calcium in the precipitate of globulin was determined by the micro method of Muntz. (5) Briefly, 2.0 ml. of the solution to be tested were mixed with 0.5 ml. of a saturated solution of ammonium oxalate. The next day, the precipitate was separated by centrifugation and washed three times with a two per cent solution of ammonium hydroxide. The washed precipitate was dissolved in 1.0 ml. of warm 1N sulfuric acid, followed by 1.0 ml. of a solution of ceric sulfate ($Ce(HSO_4)_4$) containing 145

TABLE I

*The Effect of Surface on the Rate of Clotting of a Globulin Fraction of Normal Plasma*

Clotting time of 0.3 ml. of normal globulin* in silicone-lined tubes containing crushed glass. Duplicate determinations

| AMOUNT OF CRUSHED GLASS | CLOTTING TIME |
|---|---|
| *mg.* | *min.* |
| 0 | ∞, ∞ |
| 30 | ∞, ∞ |
| 100 | 77, 180 |
| 150 | 16, 38 |
| 250 | 8, 18 |

* The plasma from which the globulin was precipitated contained 3 platelets per mm.[3]

mg. per 100 ml. of 1N sulfuric acid. The light absorption of the mixture was then read at a wavelength of 360 mμ in a 1 cm. Corex cell in a Beckman DU spectrophotometer.

## RESULTS

### (1) *Effect of Surface on Coagulation of the Globulin Fraction of Normal Plasma*

The effect of silicone and glass surfaces on the rate of clotting of the globulin fraction was studied. In repeated experiments it was demonstrated that the globulin prepared from normal platelet-deficient native plasma failed to clot when it was protected from contact with glass surfaces. However, clotting was observed regularly when normal globulin was incubated in the presence of crushed glass. Although the clotting time varied considerably, coagulation usually appeared to be complete within 90 minutes after the addition of the globulin to the crushed glass. The rate at which clotting occurred depended upon the amount of glass present (Table I). In these experiments, clotting

[1] Bovine Thrombin was obtained through the courtesy of Parke, Davis and Co.

seemed to be the result of the activation of some substance in the globulin fraction upon contact with glass. The globulin prepared from oxalated plasma clotted as readily as that prepared from native plasma.

The globulin fraction precipitated by the acidification of dilute plasma is known to contain prothrombin, fibrinogen, accelerator globulin and the precursor of plasma thromboplastic factor. When a solution of thrombin was added to the globulin of normal plasma, the clotting time was the same in silicone-lined tubes and in tubes containing crushed glass (Table II). It was evident, therefore, that the glass did not influence the rate at which the

TABLE II

*The Effect of Surface on the Clotting of the Globulin Fraction by Thrombin*

Clotting time on addition of 0.1 ml. of thrombin to 0.3 ml. of globulin

| SURFACE | INITIAL CONCENTRATION OF THROMBIN (N.I.H. UNITS/ML.) | | | | |
|---|---|---|---|---|---|
| | 50 | 25 | 12.5 | 3.1 | 0 |
| | *Sec.* | *Sec.* | *Sec.* | *Sec.* | *Sec.* |
| Silicone | 12 | 19 | 34 | 140† | ∞ |
| Glass* | 10 | 19 | 35 | 160† | 7,200 |

* 250 mg. crushed glass.

† Partial clots.

TABLE III

*The Effect of Surface on the Clotting of the Globulin Fraction by Rabbit Lung Thromboplastin and Calcium*

Clotting time on addition of 0.3 ml. thromboplastin and 0.3 ml. 0.0075 M calcium chloride to 0.3 ml. globulin

| SURFACE | INITIAL CONCENTRATION OF THROMBOPLASTIN | | | | | | |
|---|---|---|---|---|---|---|---|
| | Undiluted | 1/2 | 1/4 | 1/8 | 1/16 | 1/32 | 0 |
| | *sec.* | *sec.* | *sec.* | *sec.* | *sec.* | *sec.* | *sec.* |
| Silicone | 22 | 23 | 28 | 30 | 38 | 54 | ∞ |
| Glass* | 22 | 23 | 26 | 29 | 36 | 50 | 7200 |

* 250 mg. crushed glass.

thrombin converted fibrinogen to fibrin. Similarly, when thromboplastin and calcium were added to normal globulin, the clotting time was the same in tubes with silicone and glass surfaces (Table III). Glass, then, did not accelerate the conversion of prothrombin to thrombin by heterologous thromboplastin. Globulin prepared from oxalated plasma from which the prothrombin had been removed by filtration through a Swinney filter did not clot on contact with glass surfaces, although such globulin could be clotted by the addition of thrombin. These experiments suggest that the clot-promoting activity of glass did not depend upon its effect on thrombin, prothrombin, or accelerator globulin.

Additional evidence that the effect of crushed glass was not the result of its action on prothrombin or fibrinogen was acquired from the study of a patient with a circulating anticoagulant. The mode of action of the anticoagulant in this patient's plasma was studied by Heinle, Weisberger, Vignos, and Holden. (6). They demonstrated that the anticoagulant did not interfere either with the conversion of prothrombin to thrombin or with the conversion of fibrinogen to fibrin. The anticoagulant appeared to inhibit the activation of the thromboplastic factor of plasma from its precursor.

The globulin fraction obtained from this patient's plasma failed to clot either in siliconed tubes or in pyrex glass tubes containing 250 mg. of crushed glass. It thus appeared that the anticoagulant present in the globulin fraction inhibited the clot-promoting effect of the glass. For this reason it seemed likely that the effect of crushed glass was not upon the conversion of prothrombin to thrombin, nor of fibrinogen to fibrin, since the circulating anticoagulant

TABLE IV

*The Effect of Surface on the Clotting Time of a Globulin Fraction of Hemophilic Plasma*

Clotting time of 0.3 ml. of globulin in silicone-lined tubes and tubes containing 250 mg. crushed glass

| SURFACE | NORMAL GLOBULIN | HEMOPHILIC GLOBULIN |
|---|---|---|
| | *min.* | *min.* |
| Silicone | ∞ | ∞ |
| Glass | 16 | 300* |

* Partial clot.

did not inhibit these steps. The experiments indicated that the glass probably affected some earlier step in the clotting process.

*(2) Effect of Surface on Coagulation of the Globulin Fraction of Hemophilic Plasma*

The effect of surface on clotting of the globulin fraction was studied in plasma obtained from each of five hemophiliacs. In two cases, hemophilic globulin failed to clot upon contact with crushed glass during a period of 24 hours. In the other 3, clotting in the presence of crushed glass was greatly prolonged compared with a normal globulin studied at the same time. The protocol of one of these experiments is summarized in Table IV. These experiments demonstrate that the clot-promoting effect of glass was dependent upon the presence in the globulin fraction of a substance present in normal plasma but deficient in hemophilic plasma.

*(3) The Effect of Calcium on the Clotting Time of the Globulin Fraction*

In the preparation of the globulin fraction under study, the calcium which was not bound to the euglobulin itself was removed by decantation. The precipitated globulin was then dissolved in barbital buffer. The concentration

of ionized calcium, therefore, was necessarily small. However, the globulin fraction itself was not devoid of calcium. In 14 experiments, the calcium content of the globulin prepared from 1 ml. of native plasma varied from 4 to 10 micrograms, about one-twentieth to one-tenth the amount normally present in whole plasma.

TABLE V

*Effect of Calcium on Clotting Time of Normal Globulin in Silicone-lined Tubes*

Clotting time on addition of 0.1 ml. calcium chloride solution to 0.3 ml. normal globulin

| FINAL CONCENTRATION $Ca^{++}$ | CLOTTING TIME |
|---|---|
| *mg./ml.* | *min.* |
| 0 | ∞ |
| 0.010 | 30 |
| 0.0175 | 5 |
| 0.025 | 3½ |
| 0.05 | 2½ |
| 0.075 | 2½ |
| 0.10 | 2½ |
| 0.15 | 2½ |
| 0.20 | 2½ |
| 0.25 | 2½ |
| 0.31 | 3 |
| 0.37 | 3½ |
| 0.44 | 3½ |
| 0.50 | 4 |

TABLE VI

*Effect of Calcium on Clotting Time of Hemophilic Globulin in Silicone-lined Tubes*

Clotting time on addition of 0.1 ml. calcium chloride solution to 0.3 ml. globulin

| FINAL CONCENTRATION $Ca^{++}$ | CLOTTING TIME | |
|---|---|---|
| | Normal Globulin | Hemophilic Globulin |
| *mg./ml.* | *min.* | *min.* |
| 0 | ∞ | ∞ |
| 0.015 | 70 | 480 = > 480 |
| 0.050 | 9½ | 80 |
| 0.15 | 5½ | 35 |
| 0.37 | 8½ | 38 |

When small amounts of a solution of calcium chloride were added to the globulin of normal plasma in silicone-treated tubes, clotting occurred in as short a time as 2½ minutes (Table V). In other words, the globulin fraction clotted in silicone tubes in the presence of ionized calcium. Clotting also occurred when ionized calcium was added to hemophilic globulin in siliconed tubes, but the clotting time under these conditions was greatly prolonged in comparison to a normal control (Table VI).

*(4) The Effect of Thromboplastin on the Clotting Time of the Globulin Fraction*

The experiments described in Sections 1 and 2 support the hypothesis that glass surfaces are capable of activating the plasma thromboplastic factor. It was also demonstrated that in the presence of ionized calcium heterologous thromboplastin accelerated clotting to the same degree in silicone-treated and glass tubes. However, when dialyzed thromboplastin was added to normal globulin without the addition of calcium it accelerated clotting in the presence of crushed glass. The clotting time of hemophilic globulin was also accelerated; at higher concentrations of thromboplastin, the clotting times of hemophilic and normal globulin was the same (Table VII). The clot accelerating effect of thromboplastin was noted particularly with dilute solutions; more concentrated solutions were sometimes inhibitory. When thromboplastin alone was added to normal globulin in silicone-coated tubes, coagulation was never observed.

TABLE VII

*Effect of Rabbit Lung Thromboplastin on the Clotting Time of Normal and Hemophilic Globulin*

Clotting time on addition of 0.1 ml. of dialyzed thromboplastin to 0.3 ml. globulin in glass tubes each containing 250 mg. crushed glass

| GLOBULIN | INITIAL CONCENTRATION OF THROMBOPLASTIN | | | | |
|---|---|---|---|---|---|
| | Undil. | 1/5 | 1/10 | 1/20 | 0 |
| | *min.* | *min.* | *min.* | *min.* | *min.* |
| Normal | 9 | 9 | 15 | 16 | 16 |
| Hemophilic | 9 | 15 | 15 | 47 | 300* |

* Partial clot.

DISCUSSION

It is an old observation that the rate at which blood clots after it is shed depends upon the characteristics of the surface with which it comes in contact. If it comes in contact with glass, blood clots promptly; but if it comes in contact with such surfaces as paraffin, collodion, or silicone, clotting is greatly delayed.

There has been vigorous speculation about the properties of these substances which can, like the blood vessel wall, keep blood fluid. Speculation has been equally vigorous concerning the effect of glass surfaces on blood and upon which components of blood glass acts. One theory is that the glass surface acts by causing the blood platelets to break down and that the disintegrating platelets bring about clotting. On the other hand there is evidence that glass surfaces potentiate the process of clotting even though no platelets are present in the sample of plasma studied. Years ago, Nolf (7) postulated that glass directly modified one or more of the components of cell-free plasma. Later,

Lozner and Taylor (1) were able to show that plasma from which the platelets had been removed clotted readily when it was placed in glass tubes but its clotting was delayed when it was kept in paraffin, collodion, or lusteroid tubes. They thought that glass activated the anti-hemophilic factor which had been described by Patek and Taylor (8). A study of the properties of plasma which was prepared without the use of anticoagulants further clarified this problem (2). The platelets were removed by high-speed centrifugation in silicone-treated tubes. The platelet-deficient plasma of normal individuals invariably clotted in glass tubes. But this normal platelet-deficient plasma either failed to clot at all or clotted only after a long delay in silicone-treated tubes. On the other hand, hemophilic platelet-deficient plasma clotted neither in glass nor in silicone-treated tubes. These data suggested that glass acted upon a plasma thromboplastic factor which was probably identical with the anti-hemophilic substance.

Further information concerning the activity of glass in the clotting process has been obtained by a study of a globulin fraction of plasma. This fraction was prepared from native plasma which had been separated from the formed elements of the blood by high speed centrifugation in silicone-treated equipment. The globulin fraction clotted in glass tubes without the addition of ionized calcium. However, when care was taken to prevent contact of the globulin with glass, clotting was never observed. The experiments which have been described suggest that the clot-promoting effect of glass is due to its action on the precursor of the plasma thromboplastic factor which is deficient in hemophilia. It is possible, however, that the site of action of glass may be at some earlier still undescribed step in the clotting process. If this were the case, one would still expect that in these experiments the clotting of hemophilic plasma would be delayed.

The globulin fraction under study was prepared in such a way that the calcium which was not bound to globulin was decanted. Nonetheless, the globulin fraction clotted. Analysis showed that the globulin contained small but measurable amounts of calcium ranging in different experiments from 4 to 10 micrograms per milliliter. These findings were susceptible to various interpretations. Perhaps under the conditions tested, calcium was not required for clotting. Or the non-ionized form of calcium was required and enough was present in the globulin itself to permit clotting to occur. Still a third possibility is that ionized calcium was necessary for the clotting process but sufficient calcium dissociated from the globulin to the barbital buffer to furnish the amount required. The data at hand do not allow one to make a final answer to this question, but it is evident that if ionized calcium is needed, the concentration required is small. When small amounts of ionized calcium were added to the globulin, clotting occurred within as short a time as 2½ minutes

even in silicone-treated tubes. Evidently in the presence of calcium, coagulation occurred in the absence of either platelets or glass surfaces. It is possible, however, that this was not an effect of ionized calcium but was the result of association of the added calcium to the globulin molecule. The difficulties involved in distinguishing between the effects of ionized and non-ionized calcium in clotting were discussed recently by Astrup. (9).

When thromboplastin derived from rabbit lung was added to the globulin fraction in silicone-treated tubes, clotting did not occur unless calcium was added. However, when normal or hemophilic globulin was mixed with dilute thromboplastin alone in glass tubes, clotting was accelerated. In these experiments, normal and hemophilic globulins behaved in a similar fashion. These studies, then, provide additional evidence that the defect in hemophilia is an inability to *form* thromboplastin in shed blood.

The experiments which have been described were all performed with plasma from which the platelets had been removed by centrifugation. The data obtained support the belief that platelets are not needed for the initiation of clotting and that plasma itself contains those factors necessary for coagulation.

## SUMMARY

(1) A euglobulin fraction of normal platelet-deficient plasma clotted in the presence of crushed glass but not in silicone-lined tubes.

(2) The euglobulin fraction prepared from hemophilic platelet-deficient plasma clotted only after a long delay compared with the globulin of normal plasma.

(3) The addition of ionized calcium initiated clotting in the normal euglobulin fraction in silicone-lined tubes. In the absence of added calcium, heterologous thromboplastin accelerated clotting in the presence of crushed glass, but not in silicone-lined tubes.

(4) The data presented lend support to the belief that platelet-free plasma contains those factors necessary for coagulation.

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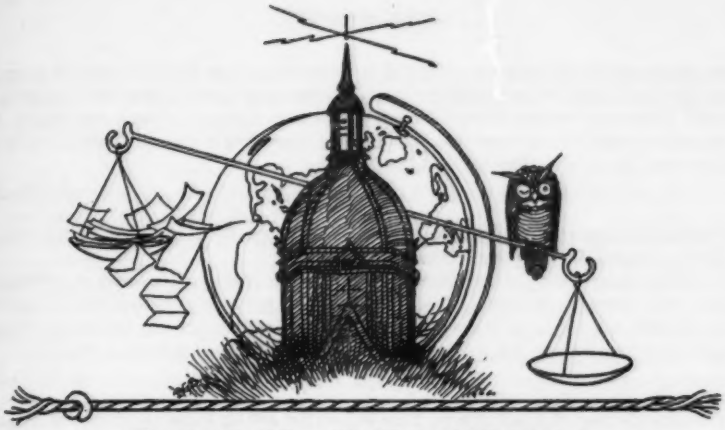

# BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

**Problems of Aging.** Transactions of the Twelfth Conference. February 6-7, 1950. Edited by NATHAN W. SHOCK. 215 pp., $3.50. *The Josiah Macy, Jr. Foundation, New York.*

The Josiah Macy, Jr. Foundation continues a splendid contribution in which a variety of scientific disciplines are brought to bear upon a common problem. The twelfth conference on aging treats the psychological and socio-economic aspects of the subject. It is an interesting sign of the times that none rose to challenge the propriety of expanding the province of medicine to include complicated socio-economic relations.

Since there is, intrinsically, nothing in this sort of material that can be measured in a spectrophotometer, everyone had an opinion. The free expression of these opinions makes this most delightful reading. The result is a revelation of the sociological bias of a group of medical investigators, all men of good will, who grappled with the vocabulary of their guests: psychiatrists, social workers, and economists. Repeatedly it is demonstrated that it is difficult for most of us to extend our sociologic attitudes beyond a frame of self-reference. A simple example of this is the fact that, although women are said to greatly outnumber men in the older population, the adjustments of aging women were considered relatively slightly by this predominantly male conference.

As is its custom at these conferences, the panel emphasized exposition of problems and lines of investigation rather than solutions. The contributions of the guest experts, at this level, were unusually lucid statements of the case.

At several points in the proceedings there were brief fundamental examinations of the rules of evidence peculiar to some of the disciplines represented. Extension of this approach would be a real service, perhaps essential to genuine appreciation of cousin sciences.

K. L. Z.

**Trends in Gerontology.** By NATHAN W. SHOCK. 153 pp., $2.50. *Stanford University Press, Stanford, California.*

This little book defies simple classification. The author, an authority in the field, undertook an inventory of gerontology with the support of the Forest Park Foundation. The results of this general survey are introduced by the familiar statistical evidences that the nation is aging. There are brief reviews of the varied activities involving, for example, employment, retirement, health, education for the aged. Then follows a listing of various research activities and "potentials" related, more or less, to gerontology. The book ends with a recommendation with which this reviewer takes strenuous issue. Dr. Shock proposes an Institute of Gerontology. Both facets of this proposal involve trends which are dismaying. The first is the centrifugal forces released within any university community

by the creation of special institutes which end by withdrawing men from the total life of the university. The second facet is the focussing of funds and efforts on research based on a specific disease or process. There is no denying the need for more information about gerontology; nevertheless, there are reasonable grounds for the view that the continued channeling of funds into special and limited categories may, in the end, allow the wellsprings to dry.

J. L. L., Jr.

**A Classified Bibliography of Gerontology and Geriatrics.** By NATHAN W. SHOCK. 599 pp., $15.00. *Stanford University Press, Stanford, California.*

This extraordinary torrent of references provides complete bibliographical data on 18,036 items. The indexing is thorough and useful. This volume furnishes not only a detailed listing of published work in the field, but even more it emphasises the ofttime forgotten fact that gerontology embraces biology in its broadest sense; it is a vast and sweeping natural science; it is not a specialty.

J. L. L., Jr.

**The Collected Papers of Adolf Meyer.** Four Volume Set $30.00. Edited by Eunice Winters. Vol. I—Neurology. Special Editor, Louis Hausman. 693 pp. *The Johns Hopkins Press, Baltimore, Md.*

The first volume of the Collected Papers of Adolf Meyer has been entitled Neurology. The division into separate parts must have been difficult for the editor. Already in this volume which deals for the most part with his earlier papers, Dr. Meyer's development of his wide-spreading psychobiologic principles is apparent and perhaps dominant. Nevertheless his interest in, and contributions to, neurology in its broadest sense continued throughout his professional life span, and this field may thus best serve as a framework for historical perspective. In this sense, the volume takes the reader through the words of Dr. Meyer from Zurich to Kankakee, to Worcester, and thence to Baltimore during the years when the writer was so strongly influencing neurologic and psychiatric thought. The progression is evident in the more strictly scientific papers and their settings. In scattered essays and reviews, however, covering most of the period, the writer and his contemporaries appear in an especially delightful fashion.

It is difficult for the current student of neurology to conceive of an approach to the subject without the brilliant postulates of "levels" by Hughlings Jackson, and their placement on more solid neuroanatomical bases by Adolf Meyer. It is apt therefore, that the present volume offers in full both the earlier comparative studies of Dr. Meyer, and also the theses in which he first formulated and developed his "segmental-suprasegmental" concepts of the nervous system. One can well imagine the impact these must have made on neurological thinking and teaching at that time. Various other representative communications on anatomical and clinical aspects have been included. The most important, of course, deals with the detour of the optic radiation in the temporal lobe which is known as Meyer's loop.

The editor and the Johns Hopkins Press are to be commended highly for making available this collection of important papers by a leader in many fields. The high standard of selection, reproduction and printing is well indicated in this initial volume.

J. W. M.

**The Neuroses. Diagnosis and Management of Functional Disorders and Minor Psychoses.** By WALTER C. ALVAREZ. 667 pp., $10.00. *W. B. Saunders Co., Philadelphia, Pa.*

The book is an interesting effort by a distinguished internist to write a work on psychiatry in medical practice. It consists of the more or less organized gleanings from the lengthy practice of a man who is highly conscious of the role that emotional and social problems played in bringing patients to his office. It is of interest to read what a person untrained in psychiatry made of these problems and how he endeavored to cope with them. It contains common sense, but it lacks the uncommon sense derived from organized experience and dynamic understanding of human motivations. The book may be of value to the practitioner by calling attention once again to the need to be cognizant of the emotional problems of patients. It is of limited value to the contemporary in-

ternist who requires sounder insights and who is, or should be, capable of utilizing the investigations of psychiatry into the nature and treatment of emotional disturbances. Its value to psychiatry can be measured only in negative terms.

T. L.

**Electroencephalography in Clinical Practice.** By ROBERT S. SCHWAB. 195 pp., $6.50. *W. B. Saunders Co., Philadelphia, Pa.*

In this small monograph the status of the specialty of electroencephalography, just now come of age, is clearly and concisely presented by the director of the Brain Wave Laboratory of the Massachusetts General Hospital, Boston. With 106 well-chosen illustrations to demonstrate his points, Dr. Schwab has described the achievements of this young specialty in language which the ordinary clinician can understand, and yet which is, in general, quite accurate technically.

A brief historical introduction gives the background and development of brain wave recording. The normal electroencephalogram is described, and the deviations from normal are discussed. The artifacts introduced by outline influences, patient or recording apparatus are illustrated in detail. The various techniques employed in clinical electroencephalography are well presented and the reader is given an insight into the methodology of workers in foreign countries.

The characteristics of the electroencephalogram in epilepsy, cerebral trauma, brain tumor, vascular lesions, and other cerebral conditions are discussed. Electrocorticography for epilepsy is presented briefly. The chapter on electroencephalography in psychiatry will be of much use to many psychiatrists. A chapter on electroencephalography in research indicates some of the avenues that have been opened by this new tool. A very useful section is appended on the organization, staffing and running of an electroencephalographic laboratory. The author points out that electroencephalography is far too complex and intricate to be undertaken by anyone who has not had proper training and does not have adequate time for the work. The interpretation of records and the writing of reports requires careful consideration so that adequate technical information is provided as well as a diagnostic opinion which may have practical value to the clinician.

There is a very useful glossary of terms appended.

This book presents in a clear, readable style a volume of information relating to the history, technique, and evaluation of data concerned in orientation in electroencephalography. Though the author states that the book is intended to be used as a basic guide for workers in associated fields, the condensed and well-chosen data could well be utilized as a guide for serious workers starting in the field.

The information is well organized. A sufficient background of neurophysiology is presented to answer the natural questions of the interested reader without becoming unduly involved. The volume is profusely illustrated with cuts of good quality. However, as the different recordings are not reduced to the same scale, a person not accustomed to such tracings could easily be confused.

The book should be read by all interested in neurology for it presents clearly and concisely the clinical significance of electroencephalography.

A. E. W.

**A Textbook of Medicine, 8th edition.** Edited by RUSSELL L. CECIL and ROBERT F. LOEB. 1627 pp., $12.00. *W. B. Saunders Co., Philadelphia, Pa.*

Textbooks of medicine for over a century have played a large role in providing basic knowledge for practicing physicians and medical students. Austin Flint, whose first edition was published in 1866, designated his as *A Treatise on the Principles and Practice of Medicine Designed for Use of Practitioners and Students of Medicine*, and William Osler in 1892 used the same title, leaving off the descriptive term treatise. It suffices nowadays to call such a volume a *Textbook of Medicine*. While the use of these volumes remains essentially unchanged this cannot be said for the contents. Whereas Austin Flint in later editions acknowledged the help of one person, namely the pathologist Dr. William H. Welch, and Osler in various editions thanked either four or five other physicians, Cecil and Loeb have ninety-six co-authors. Robert F. Loeb now serves as co-editor and seventeen new names have been added to the list in this eighth edition. Although the technique of multiple author-

ship produces a polycellular, somewhat uneven volume, it has the advantage of providing an authoritative and very nearly up to date text. Advances in knowledge are presented with critical judgment so that the reader need not fatigue himself by attempting to distinguish persuasive fancy from established fact. The co-authors have been well selected and in many instances are individuals actively engaged in investigation of the subjects they cover.

One must go back and read his Flint or his Osler to realize the profound change that has taken place in the concept of disease states, a change from the correlation of symptoms with cellular pathology to the explanation of the cellular pathological physiology involved in various symptom complexes. What a change, also, from Osler's therapeutic nihilism.

The scope of this textbook is wide but for the most part the chapters are condensed and devoid of controversial discussion. It is surprising, for instance, to see what can be done in seven pages with a subject like Congenital Heart Disease. The inclusion of recently defined esoteric but theoretically significant conditions such as phenylpyruvic oligophrenia is an example of the authors' interesting concept of a textbook exposition of medical science.

The brief bibliographies usually include both classical and recent references.

This is an extremely good book, and I can think of no medical man or student of medicine who will not find great value and interest in using it as a basis for quick reference or for initiating the study of any current subject.

H. M. T., Jr.

**Medicine of the Year 1951,** 3rd issue. Editorial Direction of JOHN B. YOUMANS. 298 pp., $5.00. *J. B. Lippincott Co., Philadelphia, Pa.*

This is an excellent series of reviews in the fields of internal medicine, psychiatry, obstetrics and gynecology, pediatrics and general surgery. A book with such a wide scope might be considered of limited value to a specialist in one of the above fields. However, the articles chosen by the assistant editors in each specialty are of such interest and so critically reviewed that they are of practical importance to anyone in any of the clinical fields mentioned above. For example discussions of articles on antibiotics can be found in each one of the above specialties except one.

The reviews of articles on potassium metabolism, salt depletion syndrome, cirrhosis and ascites, evaluation of drugs, coronary heart disease, dermatology, toxemias of late pregnancy, kernicterus, anticonvulsant drugs, pancreatitis, exophthalmos, and thoracic surgery are particularly interesting. ACTH and cortisone therapy is evaluated cautiously and not overly enthusiastically. It is regrettable that in the section on psychiatry the increasing carelessness in the choice of cases by some psychiatrists for electroconvulsive therapy is not emphasized. There is apparently a publishing error when the articles relative to carcinoma of the uterus are discussed under the heading Breast Feeding.

This book is recommended to anyone interested in clinical medicine.

P. F. W.

**Annual Review of Medicine, Vol. II.** Edited by W. C. CUTTING. Associate Editor H. W. NEWMAN. Editorial Committee, A. BLALOCK, J. S. L. BROWNE, A. M. BUTLER, E. M. MACKAY and S. C. MADDEN. 485 pp., $6.00. *Annual Reviews, Inc., Stanford, California.*

The great post-war increase in the volume of medical research in this country has made the job of absorbing and digesting the new material greater than ever before. The *Annual Reviews* attempt to expedite this absorptive process by totaling up the various important contributions of the last year or two. This second volume follows exactly in the pattern of the first. You may find summary statements of who says what about a particular new antibiotic; how much attention is now being paid to the syndrome of cervical discs, or in how many different gastrointestinal conditions banthine is now popular.

Thus these reviews will continue to be primarily of value as a guide to the literature. Exceptions to this limitation are the chapters by Burnet on "Viral and Rickettsial Diseases" and, in particular, "Laboratory Aids to Diagnosis and Therapy" by J. P. Peters. On "Nutrition and Nutritional Diseases," A. P. Meiklejohn and R. Passmore from the University of Edinburgh have made a special effort to review critically and have concentrated in particular on "kwashiorkor," a new de-

ficiency syndrome noteworthy in the tropics, medicine in a famine and the metabolism of ascorbic acid.

F. B. B.

**The Doctor. His Career. His Business. His Human Relations.** By STANLEY R. TRUMAN. 151 pp., $3.00. *The Williams & Wilkins Co., Baltimore, Md.*

As suggested by the title the scope of this work is wide. The book is excellent and should be perused both by medical students and physicians—particularly those interested in the practice of medicine. It states quite clearly some of the most important problems faced in the practice of medicine by the patient as well as the physician. The author has applied much careful thought to many practical medical problems in which medical schools provide little if any guidance. The discussions range from consideration of the respective advantages and disadvantages of city and country practice, medical insurance and savings, to group versus individual practice. The statements of the author are quite objective and appear well-founded. This book is recommended to anyone interested in the practice of medicine.

P. F. W.

**The Infectious Diseases of Domestic Animals,** 2nd edition. By WILLIAM ARTHUR HAGAN, and DORSEY WILLIAM BRUNER. 920 pp., $8.00. *Comstock Publishing Co., Ithaca, New York.*

There are two large reasons for an interest, on the part of a physician, in the diseases of animals. The first and practical one of these concerns the possible transmission of infection from the domestic animal to men. This is important and of increasing complexity. Although the number of people who acquire such infections as bovine tuberculosis and brucellosis is on the wane, yet the known types of infection which involve both man and animals has greatly increased in number. For instance, among the rickettsia there is "Q" fever, among the fungi is histoplasmosis—first described as a fungous infection in a dog. Among the viruses are a variety of members of the psittacosis-lymphopathia group, several of the encephalitides and Newcastle disease of chickens. These infections are clearly and simply described in this book and the effect of the infection of man briefly presented. In line with this are several excellent photographs, such as milker's nodules from cowpox, i.e. naturally acquired vaccinia.

A more important reason for medical interest in this book is the amount of basic biology of disease contained herein. A number of medical men have made outstanding contributions to animal pathology. Practically every chapter in this book refers to some discovery of Theobald Smith, from the transmission of tick fever to the discovery with Salmon of the bacteria later called Salmonella. Studies on passive immunity of the new-born were furthered by the discovery of the immunizing power of colostrum. More recently Shope's studies of swine influenza and the virus etiology of papillomas and fibromas in rabbits are outstanding discoveries.

Every physician interested in infectious diseases will want to know about this book and will find it useful and thought-provoking.

F. B. B.

**Physiology of the Eye. Clinical Application.** By FRANCIS HEED ADLER. 709 pp., $12.00. *The C. V. Mosby Co., St. Louis, Missouri.*

This book is a worthy successor to Adler's *Clinical Physiology of the Eye* which was published in 1933. For a number of years the original book was the standard American textbook for students of ophthalmology and for practising ophthalmologists, the material therein being clearly and simply presented, always with the aim of correlating the physiology of disease processes with therapy based on the pertinent physiological processes.

The aim of this original book is carried over to the new text but, as the author explains, knowledge of the subject has so increased that an entirely new book rather than a revision was demanded. The dynamics of aqueous humor formation, photochemistry of the retina, and the application of electrophysiologic techniques to retinal function are examples of material in basic physiology that required fresh treatment. The text offers the recent findings in the physiology of the eye gleaned from the experimental laboratory and applies these facts clinically.

The eyelids, lacrimal apparatus, cornea, aqueous humor, intraocular pressure, iris and pupil, lens and vitreous, accommodation, ocular circulation, and ocular motility each occupy a chapter.

The chapters on aqueous humor, the lens, and portions of the chapter on the cornea were written with the help of Dr. V. Everett Kinsey, whose research in these fields is well known, and who, with other research scientists whose work is reviewed by Adler, is setting the pace for ophthalmic research using recently developed techniques. The motility of the eye is discussed in a chapter of 143 pages and is unique because of the author's continued fundamental research on muscle physiology.

The remainder of the book deals with the physiology of vision, starting with the nature of light, tracing the photochemical and electrical events in the retina, describing the visual pathways and discussing finally the physiological and psychological aspects of vision.

The bibliography at the end of each chapter includes references to original sources of information and should help the reader pursue a comprehensive study of each of the basic subjects discussed. The book is greatly enhanced throughout by the application of knowledge in ocular physiology to clinical problems as interpreted through the rich clinical experience and seasoned judgment of the author.

S. R. L.

**A History of Nursing,** 2nd edition. By GLADYS SELLEW and C. J. NUESSE. 439 pp., $3.75. *The C. V. Mosby Co., St. Louis, Missouri.*

This is a revision of *A History of Nursing* published by the same collaborators in 1946. It is designed as the previous edition was, as a textbook for undergraduate nurses.

It presents the development of nursing in its general historical context from primitive society to the present. Inevitably, all histories of nursing introduce side glances at the mise en scène. But the attempt here is of a different nature. The book reviews the main sociological features of the various epochs of history prelusive to a description of the kind of nursing that flourished within them.

To essay so much attracts admiration for the very boldness of the design, the more so as the authors have mastered their material into such concise form.

Yet, inherent in a conception so considerable are difficulties. The inner balances of the plan fall open to question. The general history up to the time of the Crimean War commands, in my estimation, a disproportionate amount of the readers attention. After that time, an even fuller exposition of the factors within society that have so radically altered the demands made on the profession would be an asset. To allude to this disproportion is in no way to detract from the value of the admirable chapters on contemporary nursing, particularly American professional developments.

In style the book lacks the brilliant incisiveness of Lucy Seymer's *A General History of Nursing,* nor has it the imaginative sense of inquiry of the Nutting and Dock. But it is an admirable text, offering a wealth of material, clearly presented.

J. Le P.

**History of the Woman's Medical College, Philadelphia, Pennsylvania—1850-1950.** By GULIELMA FELL ALSOP 256 pp., $4.00. *J. B. Lippincott Co., Philadelphia, Pa.*

Dr. Alsop, a graduate of the class of 1908 of the Woman's Medical College, has presented in detail the history of the first medical college for women in history and the only medical college for women in America. The history of its difficult beginning and difficult survival up until its modern development is described in great detail. Dr. Alsop has very vividly pointed out the many difficulties which the temper of the times imposed upon the early beginning of the medical college and the assistance that was obtained from men who believed in women's abilities and greatly aided the cause of the Woman's Medical College. It is obvious in this history that the leaders of the Woman's Medical College were women who realized that the social and professional position of the women medical students and graduates would depend upon themselves.

Dr. Alsop describes in detail the incorporation of the Female Medical College of Philadelphia in 1850 and describes in succeeding chapters the achievements of the Deans of the Medical College. The Florence Nightingale plan for training nurses appealed to both Drs. Ann Preston and Emeline Horton Cleveland, so that in 1863 a course in nurses training was begun as well as a short course in